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MARCH 15, 1983

The American Journal of CARDIOLOGY®

25th Anniversary

35

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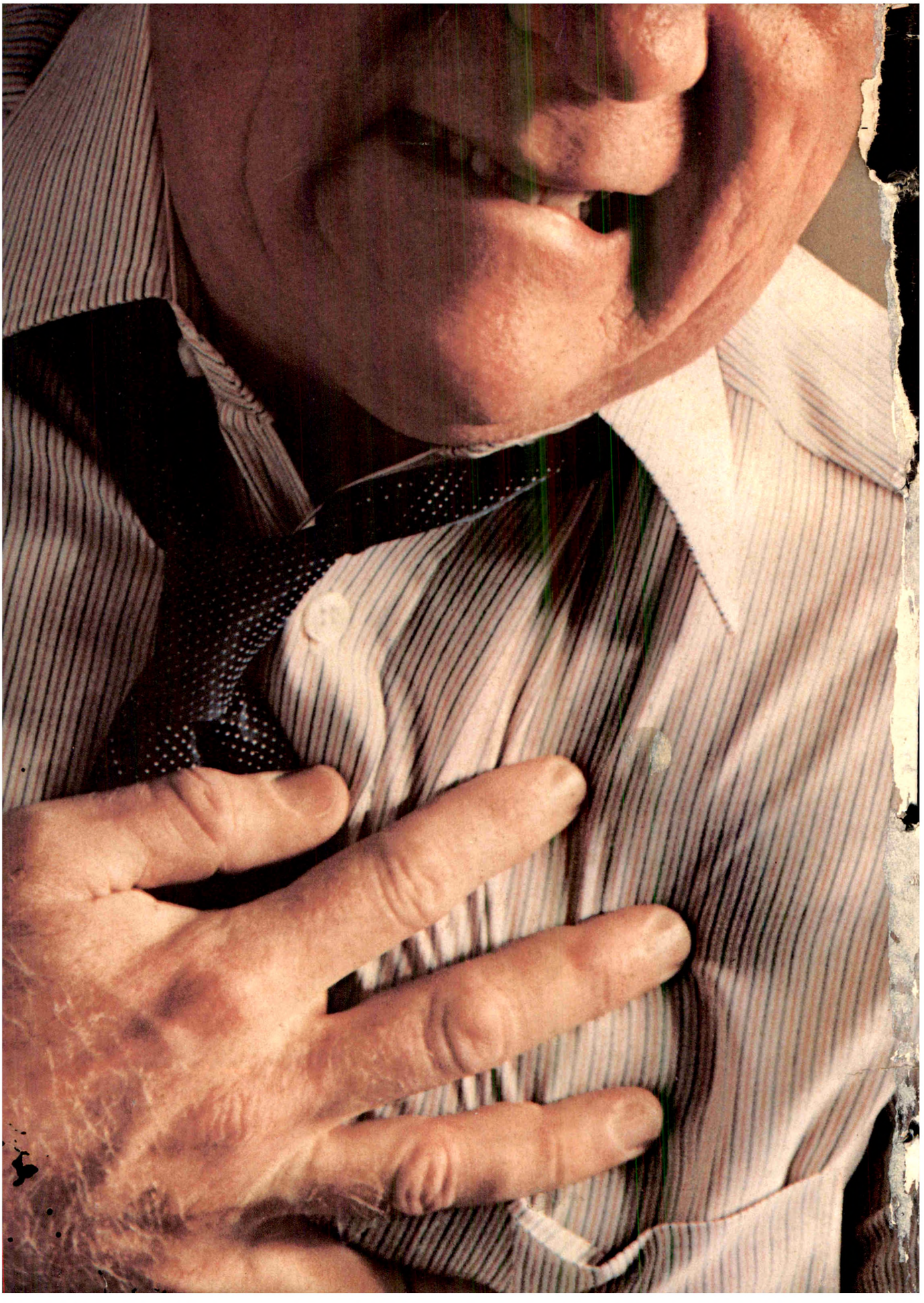

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INDERAL® (PROPRANOLOL HCl) TODAY CAN TAKE THE CONCERN OUT OF TOMORROW.

Fewer angina attacks, less anginal pain, greater freedom from fear. That's what early use of INDERAL (propranolol HCl) can mean to today's angina patients. INDERAL works to reduce myocardial oxygen demand—by lowering the heart rate... reducing systolic blood pressure... decreasing contractility. Because it helps balance myocardial hemodynamics, INDERAL enables selected patients to do more—with less need for nitroglycerin, less fear of pain. When conventional measures are inadequate, prescribe INDERAL for angina early. INDERAL does more—so your patients may do more.

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Please see following page for Brief Summary of Prescribing Information.

P 24,135

INDERAL®
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THE MOST WIDELY PRESCRIBED BETA BLOCKER IN THE WORLD.

NEW TABLET SHAPE

The appearance of these tablets is a trademark of Ayerst Laboratories.

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

TABLETS
—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-99). Also in unit dose package of 100 (NDC 0046-0421-91).
—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-99). Also in unit dose package of 100 (NDC 0046-0422-91).
—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-99). Also in unit dose package of 100 (NDC 0046-0424-91).
—Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-99). Also in unit dose package of 100 (NDC 0046-0428-91).
The appearance of these tablets is a trademark of Ayerst Laboratories.
Store at room temperature (approximately 25° C).

INJECTABLE
—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).
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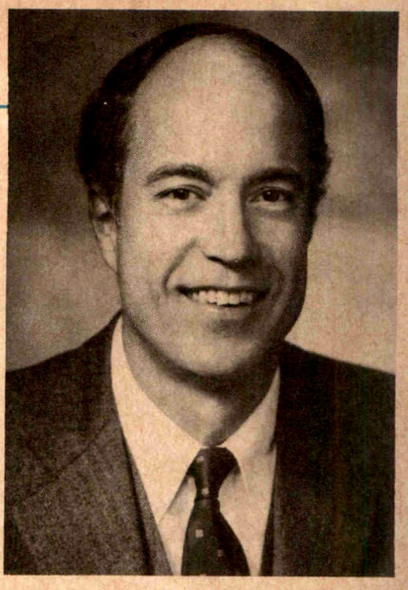
FROM THE EDITOR



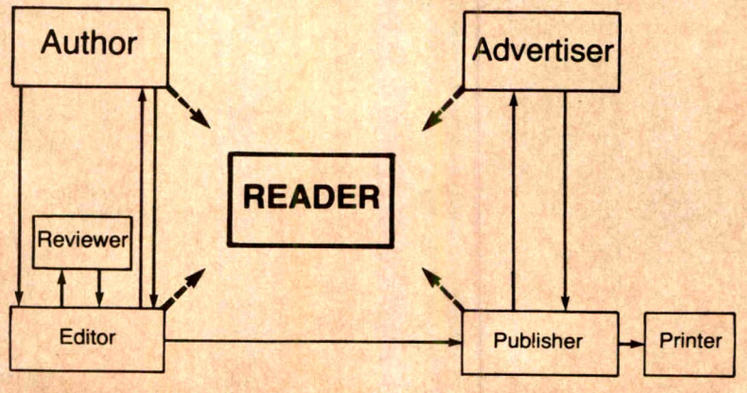
Author-Advertiser: Their Dependency on One Another

Occasionally I hear a physician complain about the number of advertising pages in medical journals. The number of medical journals, however, would be few and very expensive were it not for the ads. If there were no advertisements, a year's subscription to the AJC instantly would be approximately twice its present cost and later, as the number of subscribers diminished because of the journal's high price, even more. Although few physicians pick up a medical journal to read ads, there would be few journals to pick up were ads not present. Thus, physicians must appreciate the enormous contribution of advertisers to their education.

All elements of a medical journal (see figure) focus on providing the reader the best available information in the most presentable form. The 2 key elements in publishing medical articles are the authors (investigators) and advertisers. Among his many responsibilities, the publisher acquires the ads; the more ads acquired, the more text pages are provided. The publisher provides the editor with text pages based on several factors, a major one being the projected number of ads to be acquired over a specified period. During the first 6 months of 1983, each monthly issue of the AJC will average 228 text pages. Three additional issues, published during this period (in January, March, and May) will average 116 pages. All 9 issues consist of original articles; symposia sponsored by pharmaceutical companies are published separately and are not included in these figures. Thus, excluding symposia, 1,716 text pages will be published during the first 6 months of 1983. Without the advertisements, the number of text pages would diminish enormously and the patient would be the ultimate loser.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief



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a major motion picture exploring the most promising advances in cardiac imaging technology and the study of perfusion and myocardial function.

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Pontchartrain Ballroom, Sections C and D
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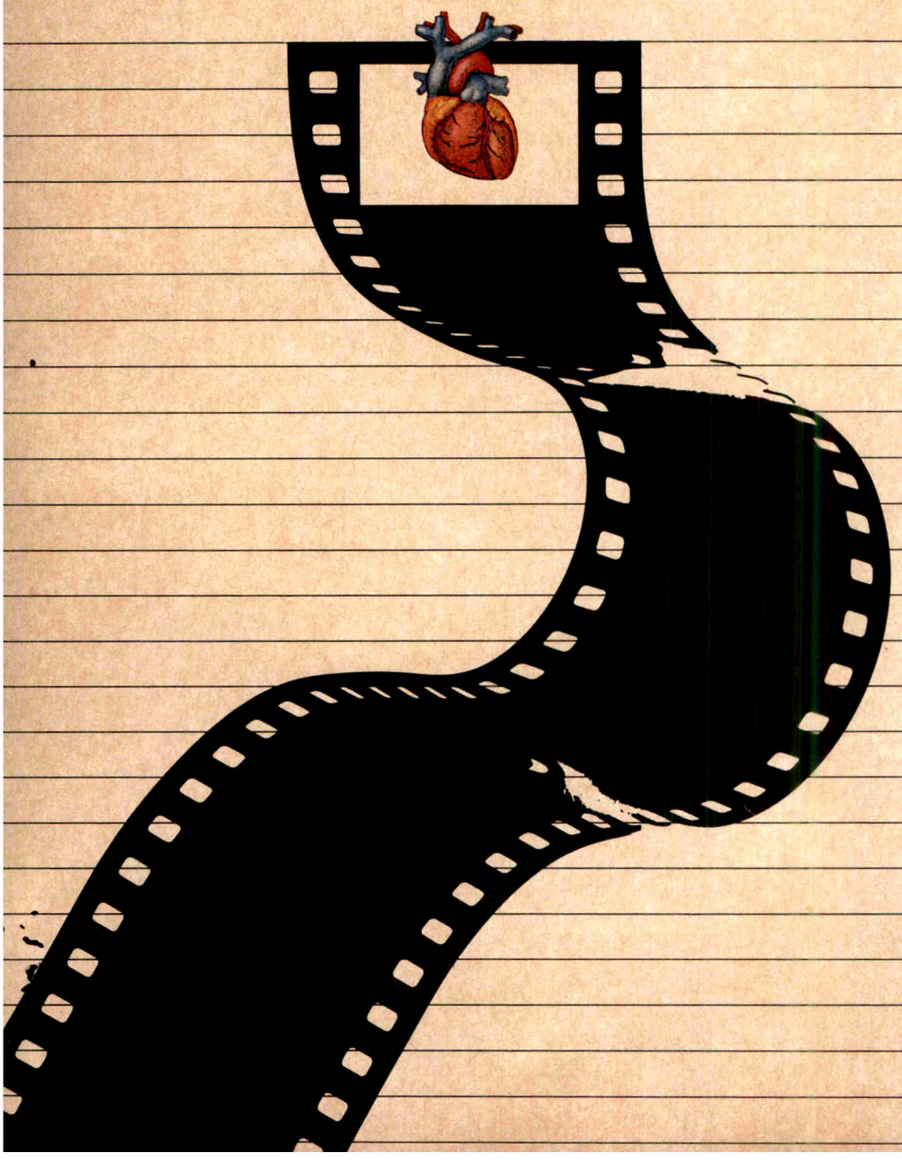
Buffet luncheon will be served. Seating will be limited to 300 people, on a first-come, first-served basis.



A panel of the investigators featured in the film will be available for questions and answers following the showing.

Participants in the film include:

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Robert J. Bache, M.D., F.A.C.C.
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As an organization accredited for continuing medical education, the University of Minnesota designates this presentation of "Perfusion & Function" as meeting the criteria for one credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association/ACCME.

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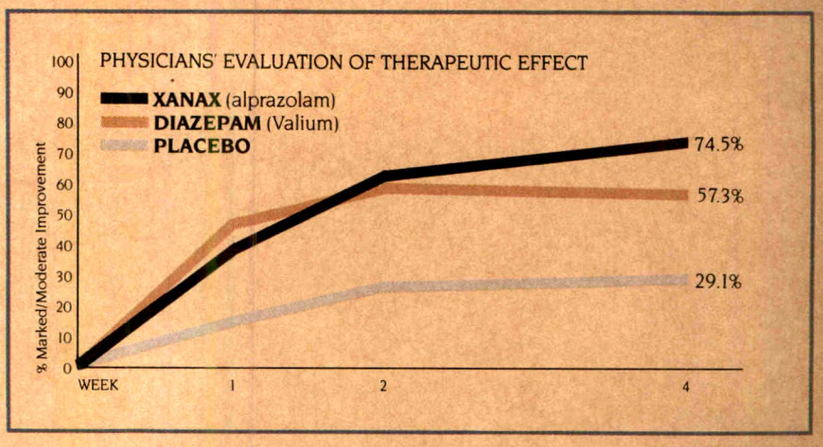
In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam (Valium).*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy (Valium) in *a 976-patient,* placebo-controlled, multicenter study.*

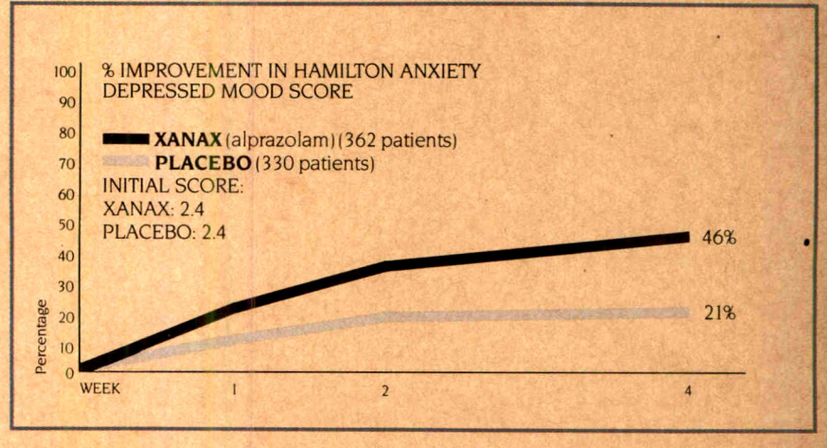


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.

The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

Xanax® 0.5 mg Tablets

alprazolam

XANAX® Tablets ℞
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about. (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 42 (9):347-351, 1981.

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J-9554 May 1982

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Indications: Premature atrial and ventricular contractions, aproxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, light-headedness, and tremor; (3) G.I. symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at the rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

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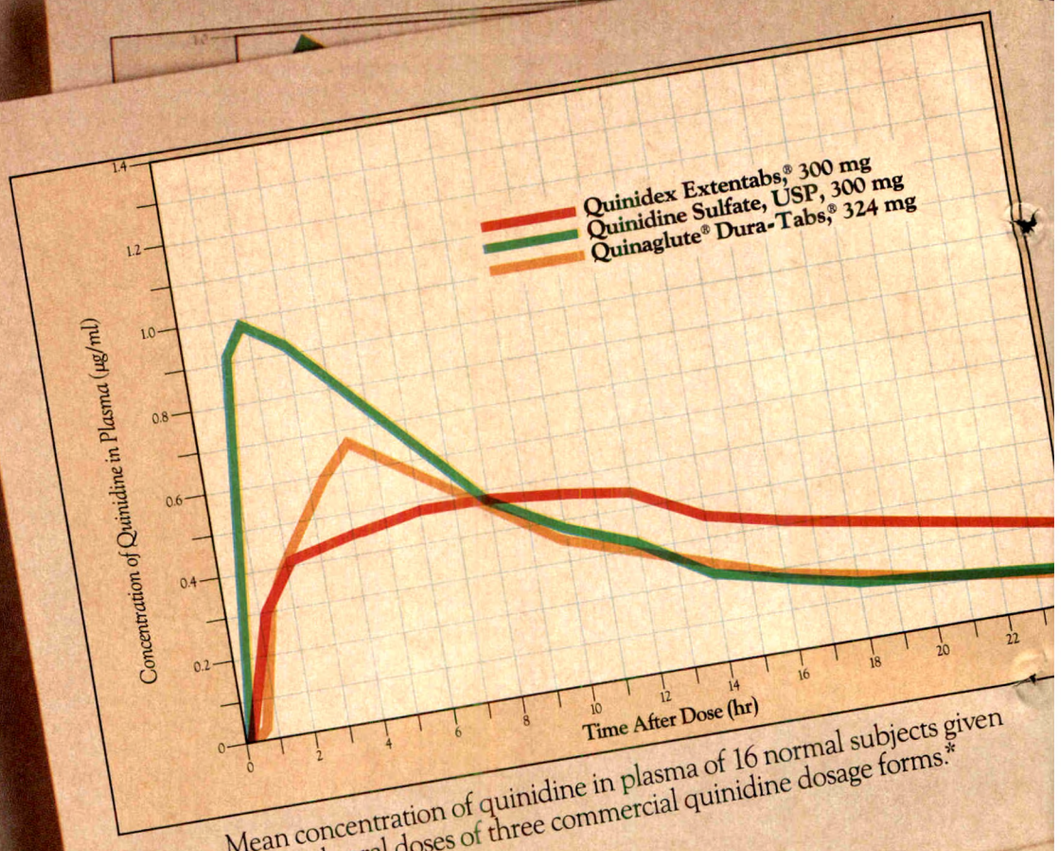

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VOLUME 51

NUMBER 6

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CONGESTIVE HEART FAILURE

919 Cleft Anterior Leaflet of the Mitral Valve With Intact Septa. A Study of 20 Cases

ELIO DI SEGNI and JESSE E. EDWARDS

Twenty pathologic specimens of heart, each with a cleft in the anterior leaflet of the mitral valve not associated with septal defects of persistent common atrioventricular canal (isolated cleft of the mitral valve), were studied. In 9 cases, there were either no associated anomalies or ones with no functional significance. In each of the other 11 cases, there were other significant cardiac anomalies associated, including ventricular septal defect and d-transposition of the great arteries. Functional consequences of the mitral anomaly were mitral insufficiency, subaortic stenosis, or the 2 together. Mitral insufficiency was related principally to the width of the cleft. Subaortic stenosis, when present, was due to the position of insertion of accessory chordae in the ventricular septum in a position under the commissure between the left and right aortic cusps or under the right aortic cusp.

927 Isolated Cleft Mitral Valve: A Variety of Congenital Mitral Regurgitation Identified by 2-Dimensional Echocardiography

ELIO DI SEGNI, JOHN L. BASS, RUSSELL V. LUCAS, and STANLEY EINZIG

Nine children aged 1 day to 12 years with cleft anterior mitral leaflet without atrial and/or ventricular septal defect of the endocardial cushion defect type were studied. One patient had 3 family members with an endocardial cushion defect. All 9 patients had an apical pansystolic murmur of mitral regurgitation (MR). The electrocardiogram showed a prolonged P-R interval in 3 patients; the QRS axis was normal in 5. Cardiac catheterization, performed in 4 patients disclosed increased pulmonary arterial wedge pressure in 2; no patient had significant subaortic stenosis. Cineangiographic left ventriculograms demonstrated severe MR in 3 patients but did not show a cleft mitral valve or goose-neck deformity in any patient. Surgical confirmation of the mitral cleft was obtained in 2 patients. Two dimensional echocardiography demonstrated the following features: The mitral anulus was normally positioned; the anterior mitral leaflet was divided by a cleft into 2 portions of different width in 5 patients and of equal width in 4; the edges of the cleft were thickened in 6 patients and of normal thickness in the 3 infants; accessory chordae tendineae extending from the basal portion of the anterior mitral leaflet to the ventricular septum were shown in 3 patients; mild narrowing of the left ventricular outflow tract was present in 3 patients; atrial and ventricular septa were intact in each patient; the mitral and tricuspid anuli were at different levels in each patient. Two-dimensional echocardiography is the only available method to reliably diagnose isolated cleft of the mitral valve clinically.

932 Pulmonary Atresia With and Without Ventricular Septal Defect: A Different Etiology and Pathogenesis for the Atresia in the 2 Types?

LYNN M. KUTSCHE and L. H. S. VAN MIEROP

Twenty-four hearts with pulmonary atresia or critical stenosis and intact ventricular septum were compared with 11 specimens of pulmonary atresia with ventricular septal defect, all from infants under 1 month of age. Distinct morphologic differences were found between the 2 groups. The pulmonary valve, although atretic, was usually well formed and the pulmonary trunk quite large in the former, whereas the valve was nearly always malformed, often reduced to a dimple, and the pulmonary trunk very small in the latter. In all cases with a small pulmonary trunk the ductus arteriosus was long, tortuous, and originated from the aortic arch in a proximal position, while in those with a normal or large pulmonary trunk the ductus usually had a normal shape. Based on these anatomic findings and present knowledge of cardiac embryology, the possible pathogenesis of these defects is discussed.

Continued on Page A15

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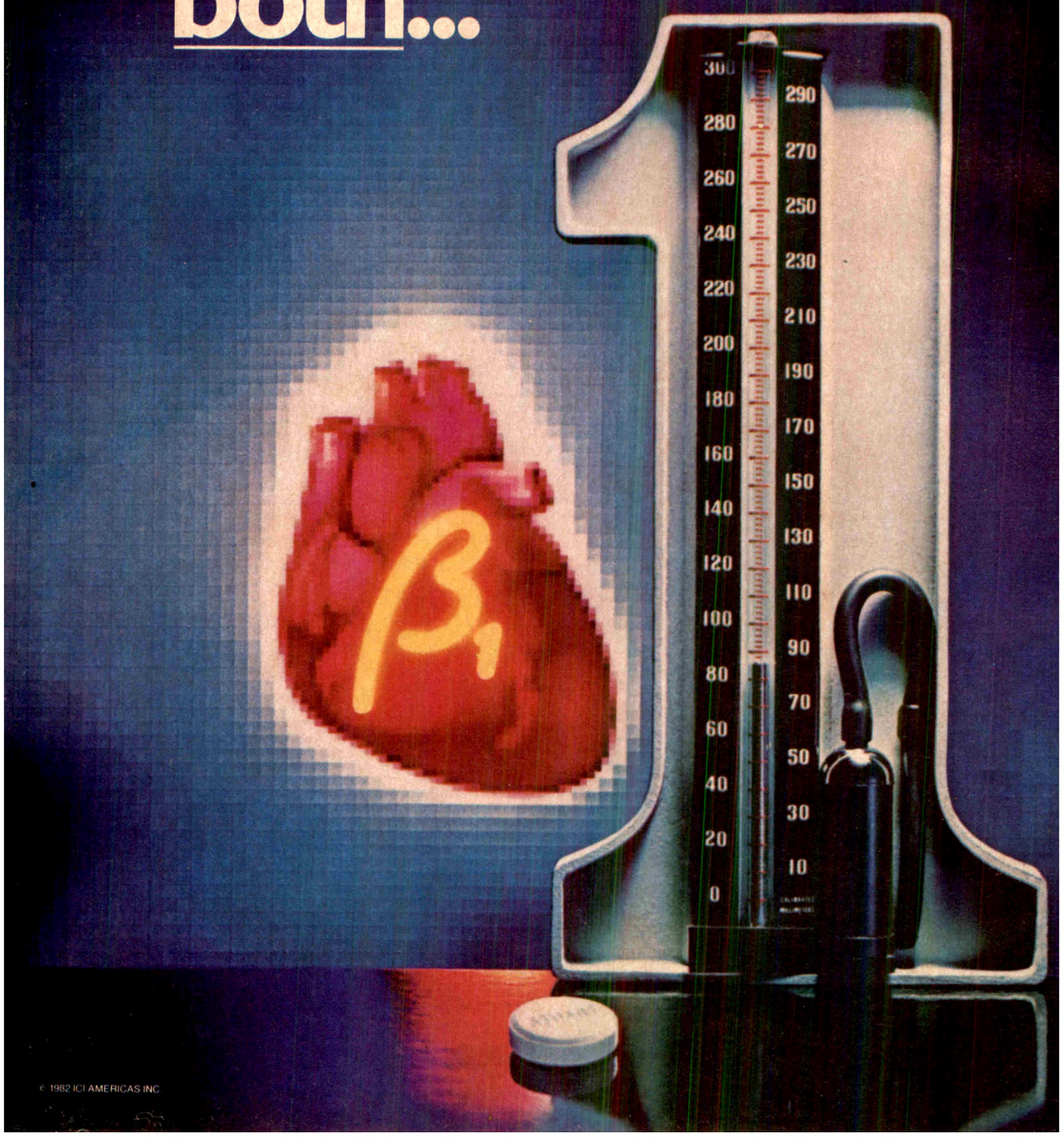

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*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

See last page of this advertisement for brief summary of prescribing information.

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A $beta_1$-selective blocking agent for hypertension.

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a $beta_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

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CONTENTS

936 Pulmonary Vein Wedge Angiography: Indications, Results, and Surgical Correlates in 25 Patients

ROBERT M. FREEDOM, GIACOMO PONGIGLIONE, WILLIAM G. WILLIAMS, GEORGE A. TRUSLER, C. A. FREDERICK MOES, and RICHARD D. ROWE

Pulmonary vein wedge angiography is a safe procedure that has been applied to 25 patients in our institute. It is designed (1) to demonstrate the presence or absence of mediastinal pulmonary arteries in patients with pulmonary atresia; (2) to determine the patency and calibre of a nonvisualized pulmonary artery when there is distal occlusion by either a shunt or pulmonary artery band; and (3) to determine the presence or absence of a mediastinal pulmonary artery in the patient with so-called isolated congenital unilateral absence of a pulmonary artery.

942 Familial Congenital Heart Disease: How Are the Various Types Related?

PIERRE CORONE, CATHERINE BONAITI, JOSUÉ FEINGOLD, SYLVIE FROMONT, and DOMINIQUE BERTHET-BONDET

The distribution of congenital heart lesions was studied in 238 families in which at least 2 members had congenital heart disease. Concordant lesions were found in 48% of the affected first-degree relatives and in 28% of the affected second- and third-degree relatives. The concordance rate was highly significant for all lesions studied in the first-degree relatives, with the exception of ventricular septal defect. Among the discordant pairs of lesions, some were significantly greater than the expected number (tetralogy of Fallot associated with ventricular septal defect, pulmonary stenosis, or transposition of the great arteries); others were significantly less frequent than would be expected on a random hypothesis (the association of ventricular septal defect with pulmonary stenosis). It is proposed that malformations which are anatomically dissimilar but resulting from the same heart segment disorder may have some common genes, and that interaction between genes may be responsible for "antagonism" between 2 defects. The embryologic segmental approach to congenital heart disease is reinforced by this genetic study.

946 Left Ventricular Wall Stress in Compensated Aortic Stenosis in Children

RICHARD DONNER, BLASE A. CARABELLO, IAIN BLACK, and JAMES F. SPANN

In order to explain the supernormal pump function usually observed in children with significant aortic stenosis (AS), parameters of left ventricular function were examined in 11 patients with AS and 10 normal children. In patients with AS, ejection fraction (0.88 ± 0.8) and mean velocity of circumferential fiber shortening (1.8 ± 0.35 circ/s) were greater than in normal subjects (0.64 ± 0.08, 1.22 ± 0.21 circ/s, respectively, $p < 0.001$). End-systolic volume index was less in patients with AS (9 ± 8 ml/m^2) than in normal subjects (27 ± 8 ml/m^2). In patients with AS, peak systolic wall stress (238 ± 51 dynes/cm^2·10^3) and end-systolic wall stress (24 ± 12 dynes/cm^2·10^3) were significantly less than in normal subjects (439 ± 85, 109 ± 30, respectively, $p < 0.001$). The ratio of end-systolic wall stress to end-systolic volume index, recently suggested as a measure of contractile function, was similar in patients with AS (3.3 ± 1.4) and normal subjects (4.3 ± 1.6). It appears that, in children with significant AS, the reduced end-systolic volume and abnormally low wall stress along with normal contractile function may explain the supernormal pump function.

952 Measurement of Systemic and Pulmonary Blood Flow and QP/QS Ratio Using Doppler and 2-Dimensional Echocardiography

STEPHEN P. SANDERS, SCOTT YEAGER, and ROBERTA G. WILLIAMS

A noninvasive method was developed for measuring systemic and pulmonary blood flow and flow ratios using 2-dimensional echocardiography and Doppler. This method compared favorably with the Fick method for estimating blood flow and Qp/Qs ratios. Outflow tract stenosis, semilunar regurgitation, and patent ductus arteriosus were the only limitations to the use of this method encountered thus far. The authors anticipate that this technique will be useful in evaluation and follow-up of pediatric and adult patients.

VALVULAR HEART DISEASE

957 Long-Term Failure Rate and Morphologic Correlations in Porcine Bioprosthetic Heart Valves

FREDERICK J. SCHOEN, JOHN J. COLLINS, and LAWRENCE H. COHN

Of 1,110 porcine bioprosthetic heart valves implanted between 1972 and 1982, 23 have had documented primary tissue dysfunction, at an average postoperative interval of 55 months. The frequency of dysfunction was 6.8% (11 of 161) for mitral and 4.1% (7 of 172) for aortic valves implanted for ≥5 years. Valves implanted for

Continued on Page A16

<5 years had a failure rate of only 0.7%. Actuarially calculated freedom from pr
7% for the mitral valve and 91 ± 4% for the aortic valve at 10 years. The most f
recovered bioprostheses was cuspal tearing associated with calcific deposits (7
plantation 66 months), but cuspal tears in the absence of calcification occurred in
months).

**965 Comparison of Late Degenerative Changes in Porcine Bioprostheses in the M
Position in the Same Patient**

CAROLE A. WARNES, MEREDITH L. SCOTT, GARY M. SILVER, CLAUDE W
VICTOR J. FERRANS, and WILLIAM C. ROBERTS

Porcine bioprostheses implanted in both the mitral and aortic valve positions sim
20 to 61 years (mean 45) were reexamined 18 to 107 months (mean 51) later. I
changes were distinctly more severe in the bioprostheses in the mitral than in the

969 Phonocardiographic Findings in Patients With Normally Functioning Ionescu-

ROMAN L. SZKOPIEC, KENNETH B. DESSER, ALBERTO BENCHIMOL, and C

Nineteen patients with normally functioning Ionescu-Shiley prostheses in the mitra
phonocardiography. In the mitral position, opening sounds were recorded with ar
to opening sound interval of 94 ms. In 8 of 11 subjects with aortic position prosthe
corded after the first heart sound at a mean Q wave to opening sound interval of
had systolic murmurs, yet no subject had a diastolic murmur which could be ascr
In contrast to other bioprosthetic valves, the Ionescu-Shiley valve has some acou
those of mechanical prostheses, and the phonocardiogram is a simple method to

**973 M-Mode and 2-Dimensional Echocardiographic Characteristics of the Ionesc
Mitral and Aortic Positions**

ROMAN L. SZKOPIEC, JEREMY TORSTVEIT, KENNETH B. DESSER, RAJEND
ALBERTO BENCHIMOL, and DENZIL K. SOLOMON

Utilizing M-mode and 2 dimensional (2-D) echocardiography, the normally functi
both mitral and aortic positions was investigated. An in vitro study indicated that th
open and closed positions during pulsatile flow. A linear tear of the anterior cus
coarse fluttering in the open position. Detachment of the anterior cusp from a su
frequency fluttering during ejection. Alteration of transducer position eliminated t
producing a configuration resembling the normally functioning valve. There was a
tween the manufacturer's specific measurements and those determined ultraso
provide information which is useful for the long-term follow-up of patients with
multiple transducer positions may be required for suitable assessment of the val
utility of M-mode and 2-D echocardiography for appraisal of valve function.

981 Aortic Valve Systolic Flutter as a Screening Test for Severe Aortic Stenosis

MICHAEL L. CHIN, ROBERT F. BERNSTEIN, JOHN S. CHILD, and JANINE K

Fifty adult patients with aortic valve disease were evaluated with 2-dimensional
or both, to determine whether the presence of high frequency systolic flutter of th
as a sign to exclude significant aortic stenosis. Aortic leaflets were clearly iden
grams in 40 patients. Nineteen of these echocardiograms demonstrated systolic fl
these 19 patients had a mean aortic valve area measured in the catheterizatior
(mean ± standard deviation). The 21 patients who showed no systolic flutter had a
± 0.3 cm^2. Systolic flutter was not seen in any patient with a valve area <1.0 cm^2.
nificantly different in the patients with clear absence of systolic flutter and those
from the aortic root precluded clear identification of the aortic leaflets. Thus aorti
M-mode echocardiography is strong evidence against significant aortic stenosis, b
ter does not allow reliable prediction of the severity of aortic stenosis.

Continued on Page A24

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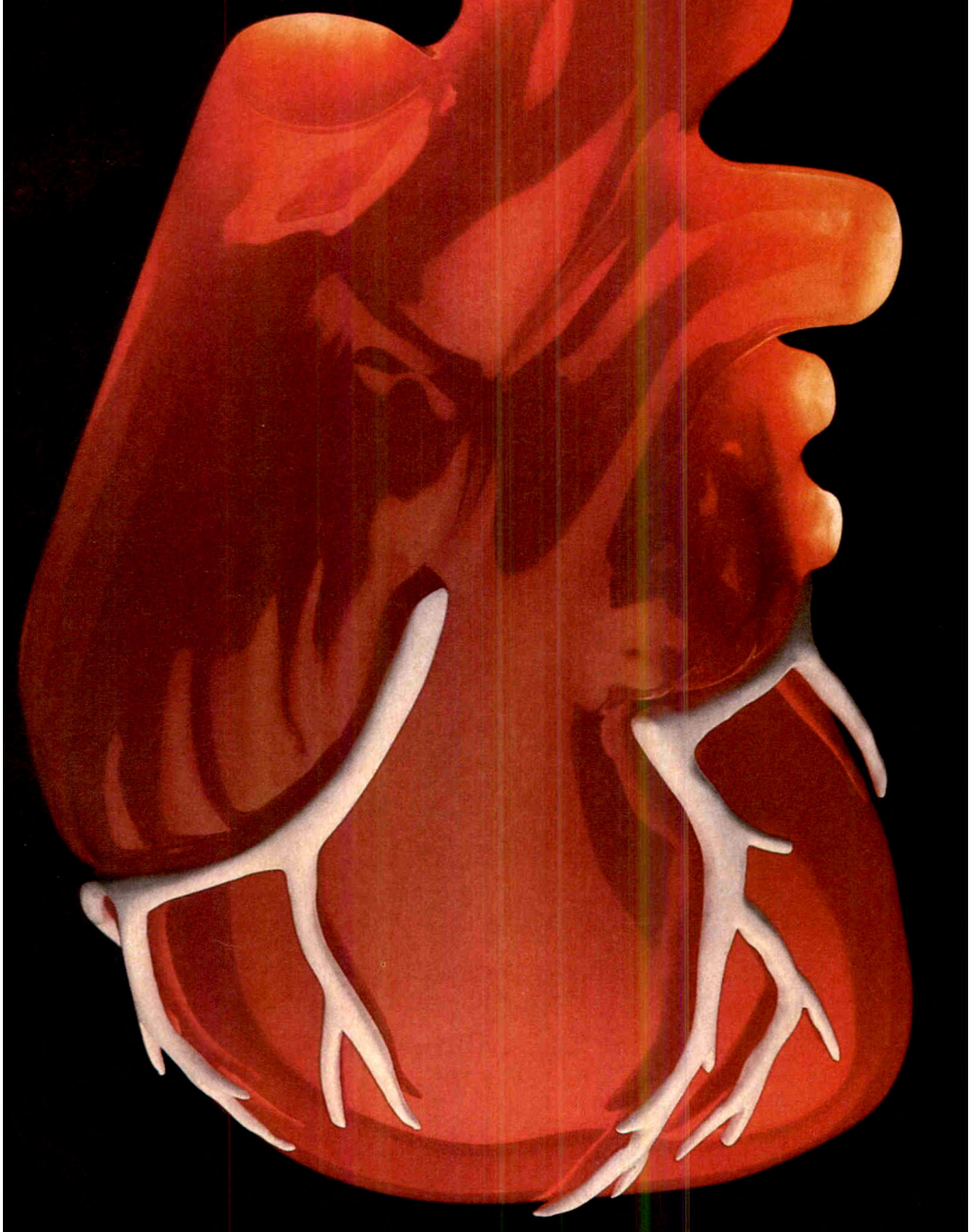
in cardiovascular therapy

New CARDIZEM™ (diltiazem HCl)

CALCIUM CHANNEL BLOCKADE
from Marion Laboratories



Potent coronary vasodilation with a
distinctive hemodynamic profile

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY WITH A LOW INCIDENCE OF SIDE EFFECTS

CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

These changes provide effective therapy with a low incidence of side effects.

Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

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CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries!

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function[3]

While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

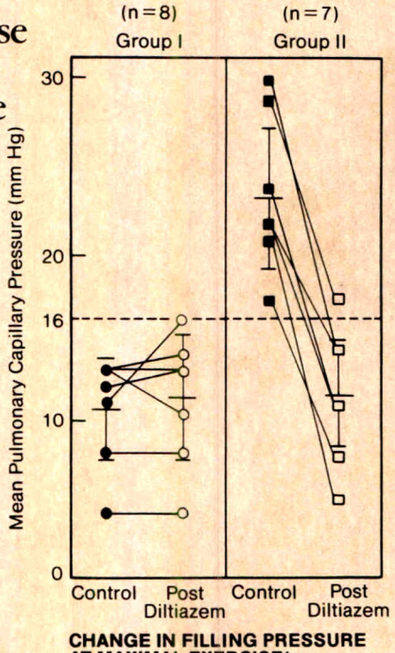
CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.

REFERENCES:

1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.



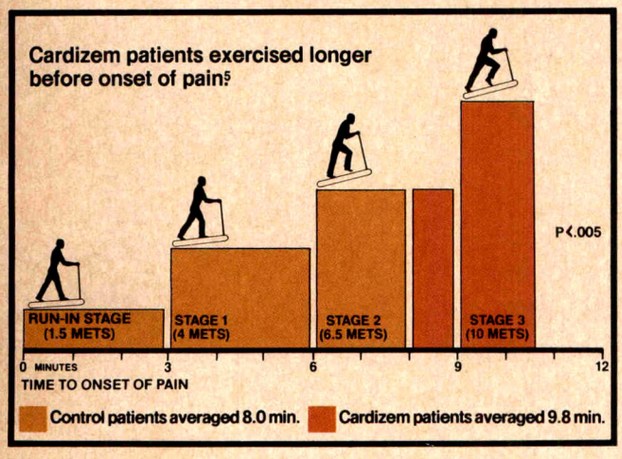
CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

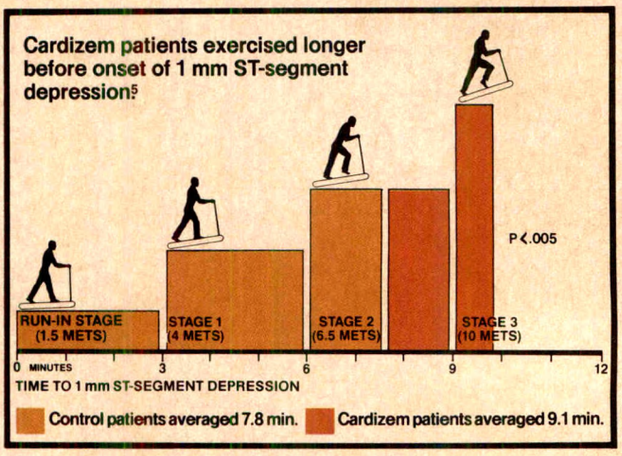
Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

Please see full prescribing information on last page of this ad.

EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:
A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

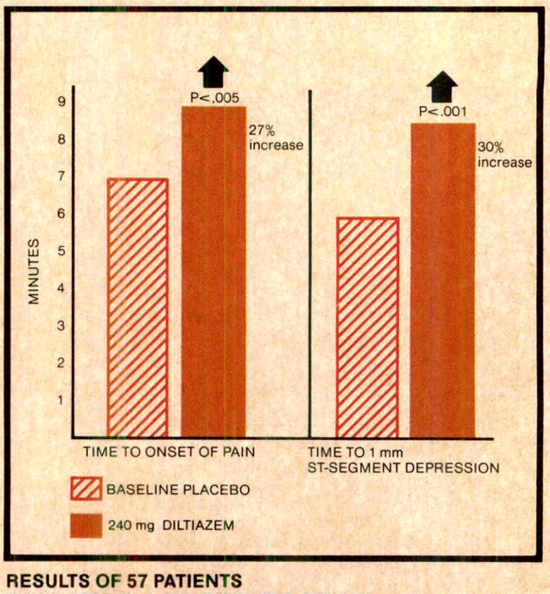
The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.
6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

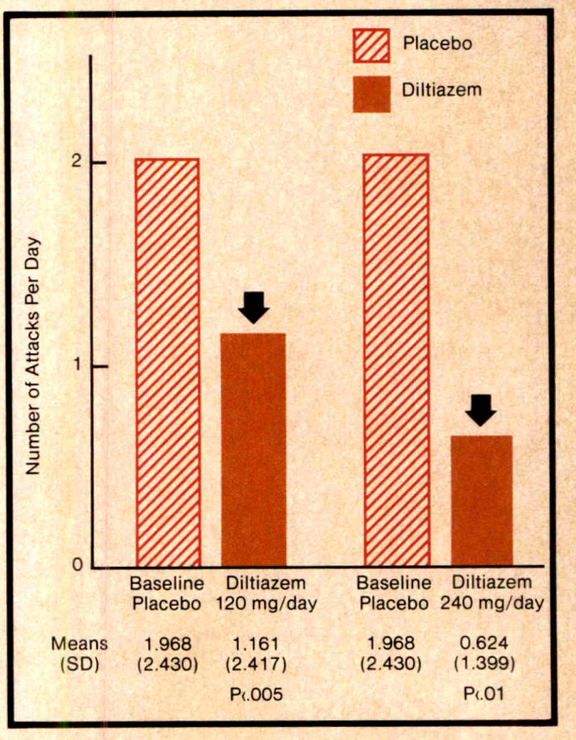
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



7. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

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cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

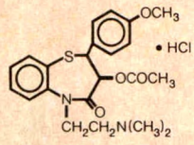
In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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986 Detection and Estimation of Rheumatic Mitral Regurgitation in the Presence of Mitral Stenosis by Pulsed Doppler Echocardiography

ASHVIN K. PATEL, GEORGE G. ROWE, JAMES H. THOMSEN, SHIRAZ P. DHANANI, PETER KOSOLCHAROEN, and LOU ELLEN W. LYLE

The sensitivity and specificity of pulsed Doppler echocardiography in diagnosing and estimating the severity of mitral regurgitation (MR) in the presence of rheumatic mitral stenosis was studied in 34 patients. When patients were classified for mild, moderate, and severe MR, the sensitivity of pulsed Doppler echocardiography for diagnosis was 54, 88, and 100%, respectively; overall accuracy was 79% and specificity 100%. Based on average systolic dispersion on a time-interval histogram, groups of patients with mild MR could be differentiated from those with moderate ($p < 0.05$) and severe ($p < 0.01$) MR; significant overlap of individual values occurred, however. In 7 of 11 patients with moderate to severe MR, systolic turbulence also was detected in the left atrium. Pulsed Doppler echocardiography was sensitive and specific in diagnosing moderate to severe MR in the presence of mitral stenosis. Assessment of the precise severity of MR is still a problem in individual patients.

992 Clinical and Echocardiographic Features of Patients With Mitral Anular Calcification: Comparison With Age- and Sex-Matched Subjects

CHANDRA K. NAIR, WILBERT S. ARONOW, MICHAEL H. SKETCH, SYED M. MOHIUDDIN, TOM PAGANO, DENNIS J. ESTERBROOKS, and TOM T. HEE

Clinical and echocardiographic features of 104 patients (53 women and 51 men) with mitral anular calcification (MAC) were compared with those of 121 age- and sex-matched controls (62 women and 59 men) without MAC. The incidence of coronary artery disease, rheumatic heart disease, systemic hypertension, and diabetes mellitus was similar in the 2 groups. Patients with MAC had a greater incidence of cardiomegaly ($p < 0.001$), cardiac conduction defects ($p < 0.001$), and aortic outflow tract murmurs ($p < 0.005$) than control patients. Patients with MAC and without aortic root calcification had a higher incidence ($p < 0.001$) of conduction defects than patients with aortic root calcification who did not have MAC. Control patients with and without aortic root calcification had a similar incidence of conduction defects. A higher incidence of atrioventricular block ($p < 0.025$) and of bundle branch block, left anterior hemiblock, or intraventricular conduction defect ($p < 0.05$) was present in patients with anterior MAC than in those with posterior MAC. In conclusion, patients with MAC have a higher incidence of cardiomegaly, cardiac conduction defects, and aortic outflow tract murmurs than a control group.

996 Prosthetic Mitral Valve Motion During Cardiac Dysrhythmias: An Echocardiographic Study

IOANNIS P. PANIDIS, JOEL MORGANROTH, DANIEL DAVID, CHIN C. CHEN, and MORRIS N. KOTLER

M-mode echocardiography was performed in 36 patients with normally functioning prosthetic mitral valves (Björk-Shiley, Starr-Edwards, and Beall valve) during various rhythm and conduction disturbances. Premature closure of the prosthetic mitral valve in diastole with a "sharp" closing motion was observed during first-degree atrioventricular block, atrial fibrillation with ventricular rates <60 beats/min, and atrial flutter. A "rounded" premature valve closure in diastole was seen during atrial tachycardia and complete heart block. These findings explain some of the mechanisms of mitral valve motion and should be considered in the echocardiographic evaluation of suspected malfunctioning prosthetic mitral valves.

VALVULAR HEART DISEASE: REVIEW

1005 Morphologic Features of the Normal and Abnormal Mitral Valve

WILLIAM C. ROBERTS

Certain anatomic and functional features of the normal and abnormal mitral valve are reviewed. Of 1,010 personally studied necropsy patients with severe cardiac dysfunction from primary valvular heart disease, 434 (43%) had mitral stenosis (MS) with or without mitral regurgitation (MR) (the etiology was rheumatic in all), and 165 (16%) had pure MR (papillary muscle dysfunction excluded). Pure MR when associated with dysfunction of the aortic valve (68 patients) was usually rheumatic in etiology, but when unassociated with aortic valve dysfunction was usually nonrheumatic in origin. Review of operatively excised mitral valves in patients with pure MR unassociated with aortic valve dysfunction and excluding papillary muscle dysfunction disclosed mitral valve prolapse to be the cause of MR in 60 (88%) patients, infective endocarditis to be the cause in 5, and a rheumatic origin in only 3. All 68 patients were >30 years of age.

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MISCELLANEOUS TOPICS

1029 Improved Cross-Sectional Echocardiographic Technique for Visualization of the Retrocardiac Descending Aorta in the Long-Axis View: Normal Findings and Abnormalities in Saccular and/or Dissecting Aneurysms

PATRICIA C. COME

An improved ultrasonic technique for visualization of the retrocardiac descending aorta is described. Excellent delineation of the aortic walls was obtained in 92% of 50 consecutive patients. Five patients with saccular and dissecting aneurysms involving the retrocardiac aorta were also examined, and abnormalities were essentially identical to those seen with computed tomography and aortography. Intimal flaps were visualized by ultrasound in all 5 patients and were seen to oscillate reproducibly with the cardiac cycle, suggesting differential rates of filling of false and true lumens.

1033 Respiratory Effects on Systolic Time Intervals During Pericardial Effusion

DAVID H. SPODICK, DELORES PALADINO, and ATHAN P. FLESSAS

Fourteen patients with pericardial effusion and no sign of hemodynamic embarrassment (specifically no pulsus paradoxus or other cardiocirculatory abnormality) had exaggerated changes in systolic time intervals during respiration compared with normal subjects and with 5 concurrent control patients with noneffusive ("dry") pericarditis. Excessive pericardial fluid may not cause clinical manifestations but is not physiologically inert.

1036 Usefulness of the Echocardiographic Right Ventricular Measurements in Estimating Right Ventricular Hypertrophy and Right Ventricular Systolic Pressure

RAVI PRAKASH and HARUO MATSUKUBO

Right ventricular wall thickness measurements were made in 111 patients by echocardiography. Anatomic and echocardiographic findings were compared in 36 subjects: right ventricular wall thickness had a sensitivity of 90% and a specificity of 94% in the diagnosis of right ventricular hypertrophy. Echocardiographic and hemodynamic findings were compared in the remaining 75 patients. The right ventricular wall thickness and right ventricular systolic pressure had a linear correlation, and estimates of right ventricular systolic pressure were fairly good ($r = 0.83$). It is concluded that echocardiographic measurements of right ventricular wall thickness are useful in estimating right ventricular systolic pressure and right ventricular hypertrophy.

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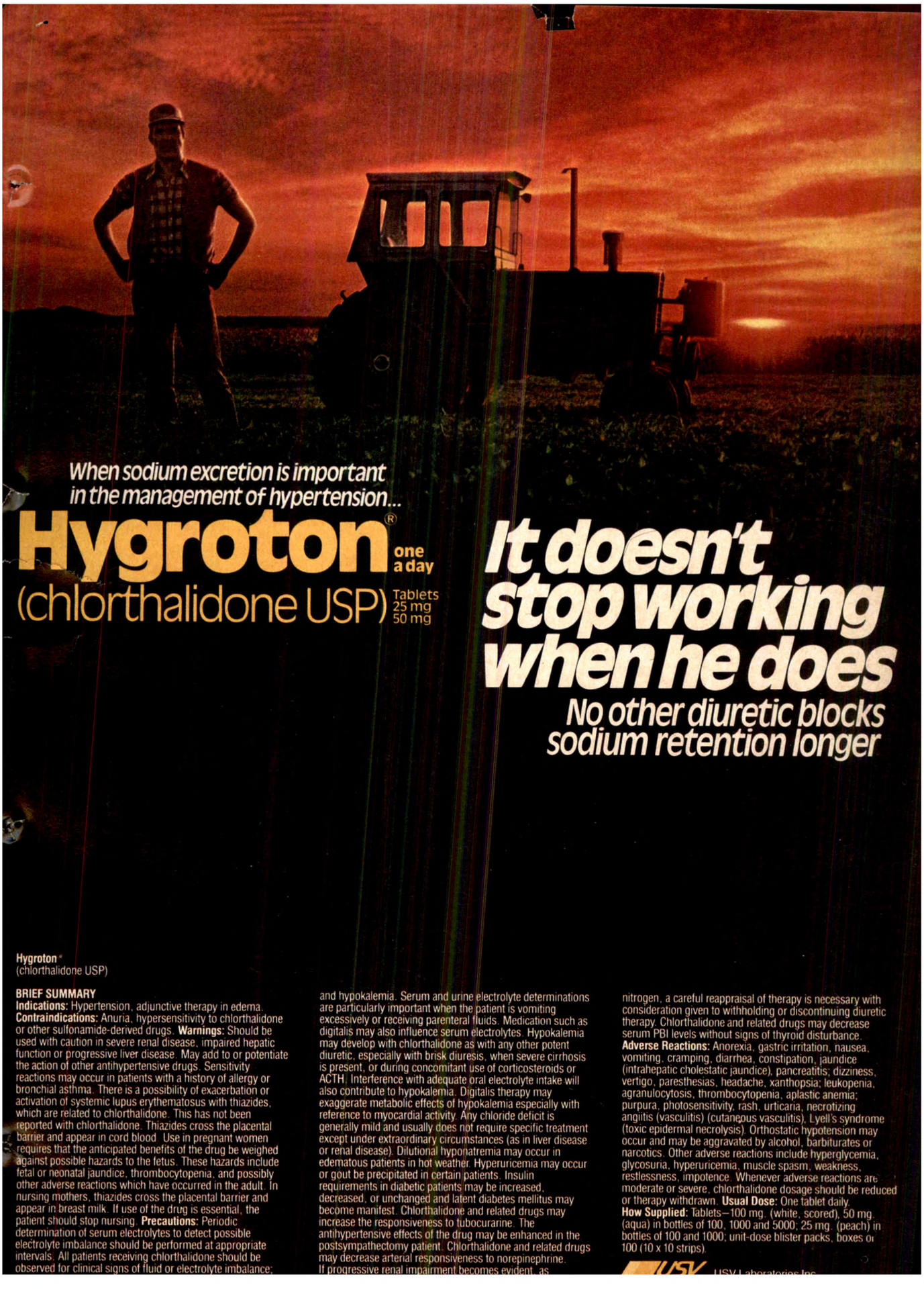

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NUMBER 6

CONGENITAL HEART DISEASE

Cleft Anterior Leaflet of the Mitral Valve With Intact Septa

A Study of 20 Cases

ELIO DI SEGNI, MD and JESSE E. EDWARDS, MD

Twenty pathologic specimens of heart, each with a cleft in the anterior leaflet of the mitral valve not associated with septal defects of persistent common atrioventricular canal (isolated cleft of the mitral valve), were studied. In 9 cases, there were either no associated anomalies or ones not of functional significance. In each of the other 11 cases there were other significant associated cardiac anomalies, including ventricular septal defect and d-transposition of the great arteries. Functional consequences of the mitral anomaly were mitral insufficiency, subaortic stenosis, or both. Mitral insufficiency was related principally to the width of the cleft. Subaortic stenosis, when present, was due to the position of insertion of accessory chordae in the ventricular septum in a position under the commissure, between the left and right aortic cusps or under the right aortic cusp.

Cleft anterior leaflet of the mitral valve, when not associated with septal defect of persistent common atrioventricular canal (so-called endocardial cushion defect) is rare. Twenty such cases observed in autopsy-derived specimens are described. A review of this material seems appropriate in that the condition is not well known, and only a few reports have dealt with its clinical and pathologic features[1–21]; the clinical recognition of this anomaly is now potentially possible with characteristics of 2-dimensional echocardiography.[21,22]

Methods

Twenty specimens of heart with a cleft in the center of the anterior mitral leaflet were available for restudy. There was an equal distribution among males and females. Down's syndrome was present in 4 cases. The ages ranged from stillborn to 74 years. The mean age at death was about 4 years. Situs solitus was present in each subject.

The specimens were derived from numerous sources over a period exceeding 22 years. The clinical data supplied to us varied. To some extent this was related to the time when any given specimen was received. Therefore, interpretation of functional consequences of the anomaly, whether mitral insufficiency, subaortic stenosis, or both were present or absent, was judged primarily from the details observed in the pathologic specimens.

Our evaluation of the anatomy of the mitral valve included measurements of the dimensions of the mitral valve and of the cleft as shown in Figure 1. Certain terms were derived from these measurements: (1) width of cleft, (2) depth of cleft, (3) width of base of anterior leaflet, and (4) depth of anterior leaflet. Certain ratios were derived from these absolute measurements.

The presence and the insertion of ectopic chordae were recorded. The position of ventricular insertion of such chordae was related to the specific overlying aortic cusps, as shown in Figure 2.

Results

The 20 cases could be classified into 2 groups as defined later (Table I). Group I consisted of 9 cases in which the cleft of the anterior mitral leaflet was asso-

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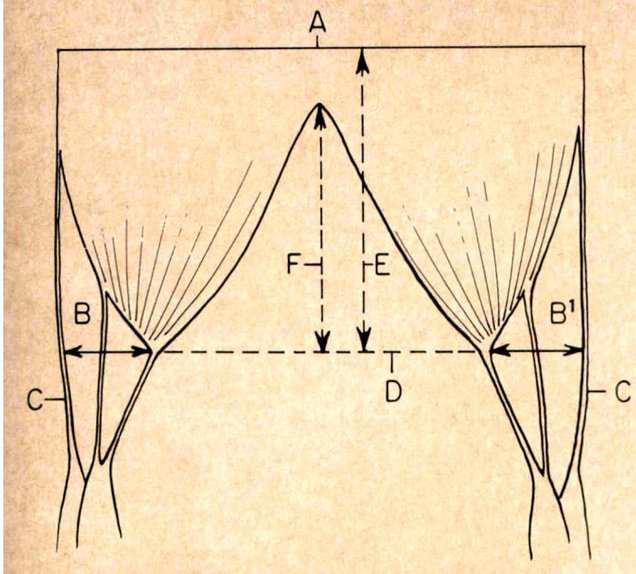

FIGURE 1. Schematic drawing of the anterior mitral leaflet showing the measurements taken. A = width of the base of anterior leaflet; B and B^1 = distance from the commissural chorda to the respective edge of the cleft; C = commissural chordae; D = width of the cleft (this width was calculated according to the formula $D = A - [B + B^1]$); E = depth of the anterior leaflet; F = depth of the cleft.

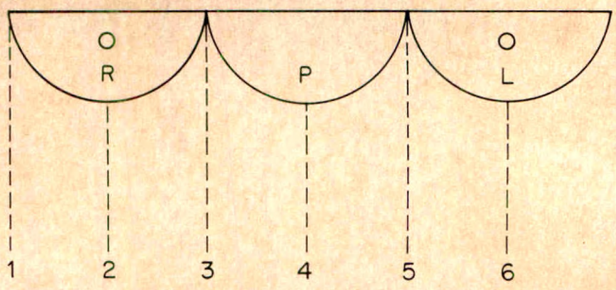

FIGURE 2. Schematic drawing showing the different positions (1 to 6) of ventricular insertion of ectopic chordae in relation to the aortic cusps. R = right, P = posterior, and L = left aortic cusps, respectively. The **circles** in R and L represent corresponding coronary arterial ostia.

ciated either with no anomalies or anomalies of minor significance. In Group I, additional anomalies were present in 4 cases. These were fossa ovalis type (secundum) atrial septal defect in 2 cases, and small left ventricular-right atrial communication and floppy tricuspid valve in 1 case each. In each of the 11 cases in Group II, a cleft in the anterior mitral leaflet was associated with other cardiac anomalies, each of significant nature. These cases were further subdivided according to whether transposition was absent or present. Thus, in our cases transposition was absent (Group IIA). Some form of transposition was present in 7 cases (6 with d-transposition, Group IIB) and 1 with classical corrected transposition (l-transposition, Group IIC). In the latter case, the cleft was in the right-sided mitral valve.

Anatomic Features of the Mitral Valve

In the normal case, the width of the base of the anterior leaflet is less than that of the posterior leaflet by a ratio of about 1:2.[23] In 13 of our 20 cases this ratio was different, the width of the anterior leaflet at its base being equal to or greater than the corresponding part of the posterior leaflet. This discrepancy from the usual was about equally distributed among cases of Groups I and II.

The leaflets of the mitral valve and the papillary muscles were normally oriented in 8 cases and rotated clockwise in 12 cases. This rotation appeared to have resulted from the abnormally posterior position of the anterolateral papillary muscle. This phenomenon was seen in 12 cases (4 of Group I, 3 of Group IIA, and 5 of Group IIB).

The cleft of the anterior mitral leaflet was usually shaped like an inverted V, with the apex pointing toward the valve ring. In 2 cases the cleft had a rectangular shape. The cleft extended for from 30 to 90% of the distance between the free margin and the base of the anterior mitral leaflet. The anterior leaflet was divided into halves except at its base, where the halves of the cleft leaflet were continuous. In 8 specimens, the cleft was located exactly in the center of the anterior mitral leaflet (Fig. 3). In the remaining cases, the cleft was

TABLE I Classification and Associated Lesions in 20 Cases of Isolated Mitral Valve Cleft

Group		Associated Defects	Cases (n)
I	The isolated cleft of the mitral valve is the predominant lesion	None	5
		Atrial septal defect secundum	2
		Left ventricular-right atrial communication	1
		Floppy tricuspid valve	1
		Total	9
II	The associated defects are predominant	IIA Ventricular septal defect	1
		Ventricular septal defect and coarctation	1
		Aortic atresia	1
		Tricuspid atresia	1
		Total	4
		IIB D-transposition of great arteries	4
		D-transposition of great arteries and tricuspid atresia	2
		Total	6
		IIC L-transposition of great arteries	1
		Total	11

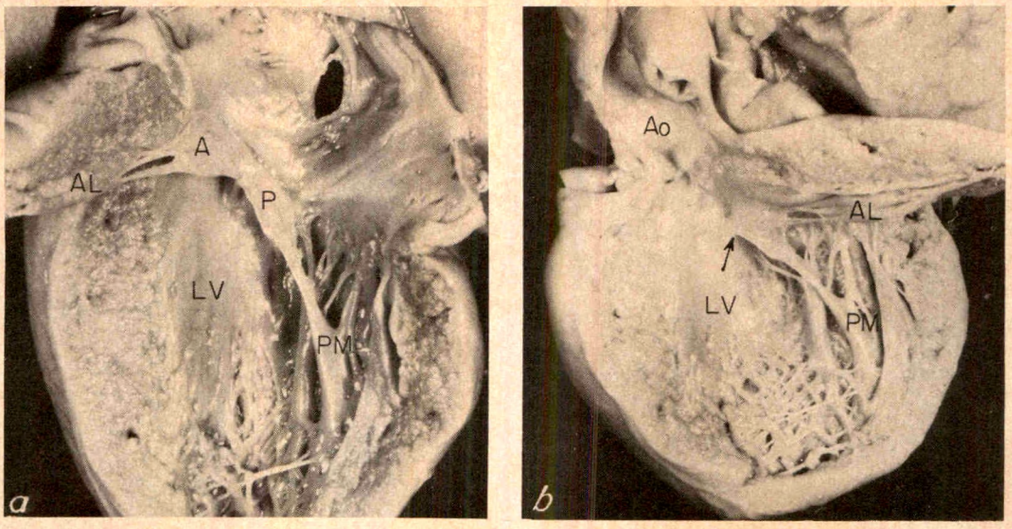

FIGURE 3. Cleft mitral valve from a stillborn infant in whom an atrial septal defect at the fossa ovalis was also present. **a,** opened mitral valve and related chambers. The cleft is in the center of the anterior mitral leaflet. The edges of the cleft are thin and smooth. **b,** left ventricle, aortic valve, and ventricular aspect of anterior mitral leaflet. A raphe-like fibrous ridge extends (**arrow**) from the anterior mitral leaflet to the ventricular septum. In both views A = anterior portion of the anterior mitral leaflet; AL = anterolateral papillary muscle; Ao = aorta; LV = left ventricle; P = posterior portion of the anterior mitral leaflet; PM = posteromedial papillary muscle.

eccentric. In 5 cases (4 of Group I) the anterior portion of the cleft leaflet was wider than the posterior. The posterior portion of the anterior leaflet was wider than the anterior in 7 cases, 4 being among the cases with d-transposition of the great arteries (Fig. 4).

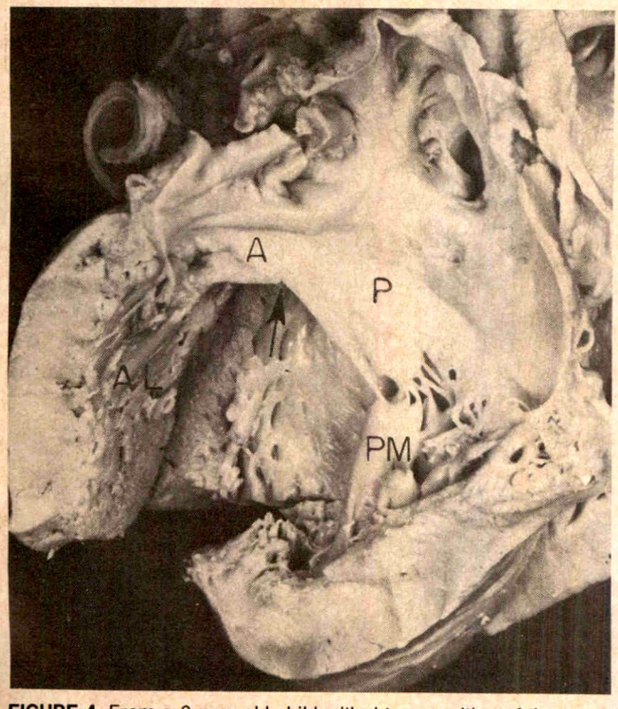

FIGURE 4. From a 2-year-old child with d-transposition of the great arteries. The atrial aspect of the cleft anterior mitral leaflet is shown. The posterior portion of the leaflet is wider than the anterior. The edges of the cleft are thin. Abbreviations as in Figure 3.

The edges of the cleft were thin and smooth in 8 specimens (Fig. 3 and 4). In the other 12 cases, the edges of the defect were thickened by nodular fibrous tissue, while elsewhere the leaflet remained thin (Fig. 5 to 7). The thickness of the edges was 2 to 4 mm in these cases. A clear positive relation existed between the ages of the subjects and the thickness of the edges of the cleft.

Normal chordae tendineae extended from the anterior portion of the anterior leaflet to the anterolateral papillary muscle and from the posterior portion of the anterior leaflet to the posteromedial papillary muscle. Accessory chordae tendineae or a raphe-like fibrous structure constantly extended from the anterior mitral leaflet to the septal or anterior walls of the left ventricle. The valvular origin of the accessory chordal tissue was into that part of the anterior leaflet that lay between the apex of the cleft and the basal attachment of the leaflet (Fig. 3 right, 5 bottom, 6 right, and 7). In only 2 cases were accessory chordae attached to the edges of the cleft (Fig. 7).

The insertion of these structures was to the ventricular septum in 16 cases (Fig. 3 right, 5 bottom, 6 right, and 7) and to the anterior wall of the left ventricle in 4 cases, each with d-transposition.

When insertion occurred to the ventricular septum it was to the membranous septum or the crest or body of the muscular septum. The sites of ventricular insertion with respect to the position of the above-lying aortic sinuses were as follows (Fig. 8): (1) insertion of accessory tissue under the commissure between the left and right aortic cusps (position 1), 3 cases; (2) under the right aortic cusp (position 2), 6 cases; (3) under the commissure between the right and posterior aortic cusps (position 3), 5 cases; (4) under the noncoronary aortic cusp (position 4), 1 case; (5) under the left aortic cusp (position 6), 4 cases.

As will be shown later, the insertion site of the chordal or raphe-like accessory tissue was a determining factor as to whether or not left ventricular outflow tract obstruction was considered present.

Associated Anomalies

In some of the cases, anomalies in addition to a cleft mitral valve were present. These are divided into 2 groups: anomalies that are either part of or frequently associated with the endocardial cushion defect, and those that appear unrelated to the endocardial cushion defect.

Anomalies related to the endocardial cushion defect: *Mitral valve:* A double mitral orifice was found in 2 cases.

Left ventricle: The ratio between the length of the outflow tract and the inflow tract of the left ventricle was as in normal hearts in 8 cases. In 12 cases, this ratio was similar to what is found in typical atrioventricular canal defects in which the inflow dimension of the left ventricle is distinctly shorter than the outflow dimension.[24]

Ventricular septum: The summit of the ventricular septum was deficient in 4 hearts, each in Group I. The muscular septum in these cases resembled the "scooped out" aspect seen in classic endocardial cushion defect (Fig. 7). This deficiency was closed by a membrane which we considered to be tricuspid tissue closing a ventricular septal defect.

Tricuspid valve: A cleft in the septal leaflet of the tricuspid valve was present in 4 hearts.

Anomalies not related to the endocardial cushion defect: Anomalies that are not considered part of the endocardial cushion defect were found in 12 of the 13

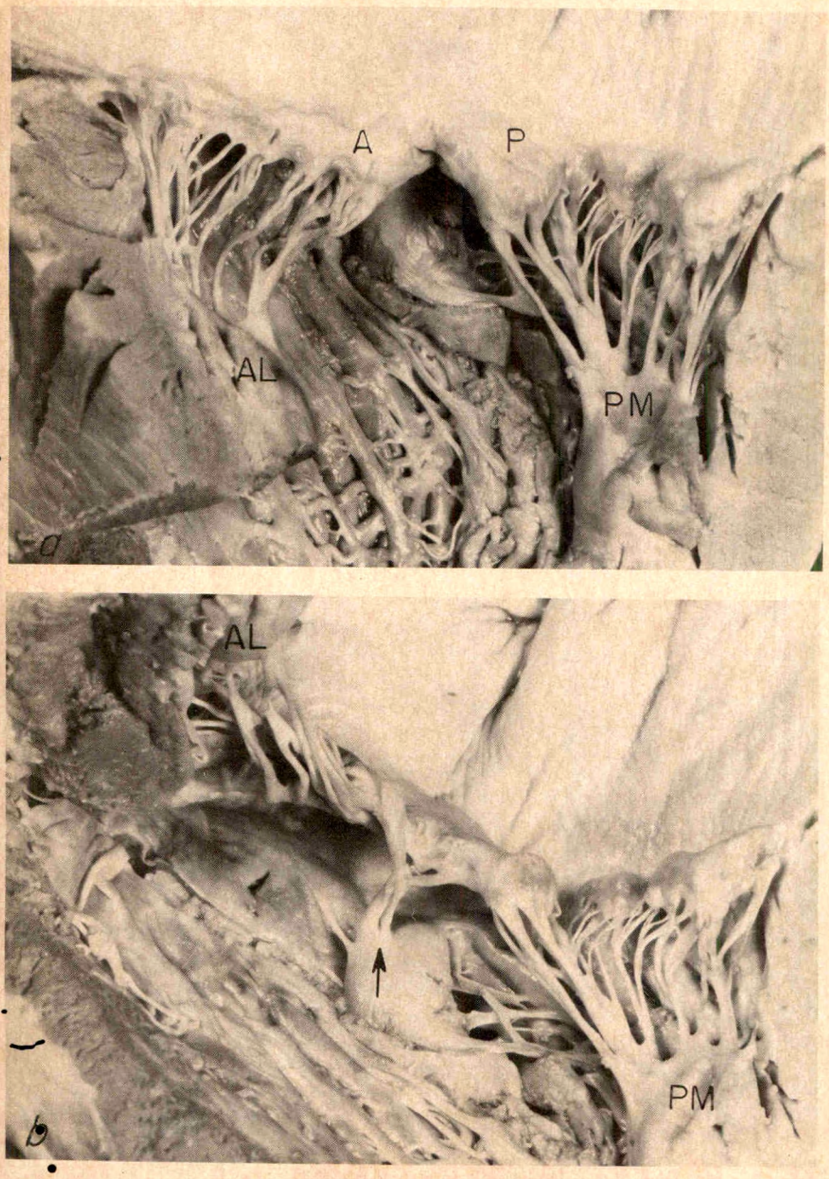

FIGURE 5. Cleft mitral valve from a 74-year-old in whom a mild prolapse of the tricuspid valve was also present. **a,** opened mitral valve viewed from the atrial aspect. The edges of the cleft are thickened by fibrous tissue, **b,** mitral valve viewed from its free edge. Accessory chordae tendineae extend from the apex of the cleft to the ventricular septum (**arrow**). Abbreviations as in Figure 3.

specimens without transposition and are listed in Table I. Of the 2 hearts with large ventricular septal defects, in each the defect was not of the so-called atrioventricular canal type. In the first of the 2, the defect was located in the area of the membranous septum. In the second case, the defect was located in the muscular septum. In the latter case, coarctation of the aorta, bicuspid aortic valve, and patent ductus arteriosus were

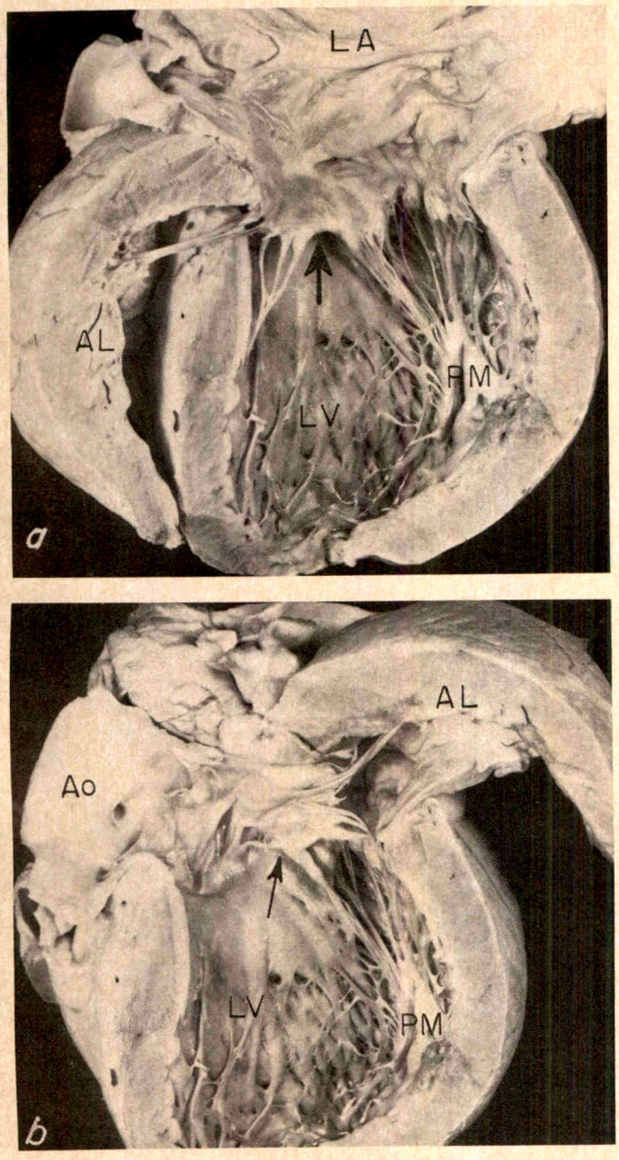

FIGURE 6. Cleft mitral valve in a 3-year-old boy with severe mitral insufficiency. **a,** atrial aspect of opened mitral valve. A shallow cleft (**arrow**) with thickened margins is present in the center of the anterior leaflet. **b,** ventricular aspect of anterior mitral leaflet from interior of left ventricle. An accessory chorda tendinea (**arrow**) and, above that, a raphe-like ridge extend from the mitral valve to the membranous septum in a position below the commissure between the right and posterior aortic cusps (position 3). In this case severe mitral insufficiency was present. This was apparently due to the restriction of the motion of the anterior mitral leaflet caused by the abnormal accessory chordae rather than to the extent of the cleft. LA = left atrium; other abbreviations as in Figure 3.

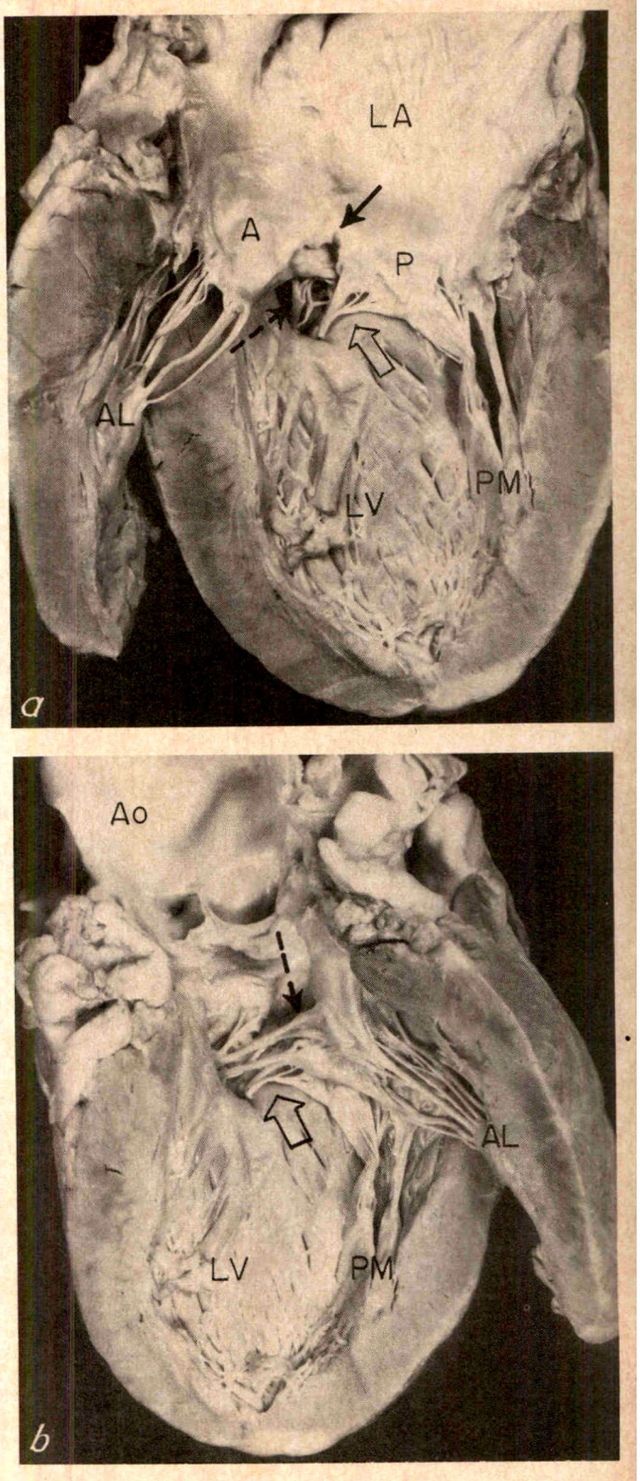

FIGURE 7. Cleft mitral valve in a 41-year-old man with Down's syndrome. **a,** opened mitral valve from its atrial aspect is shown. **a,** the ventricular aspect of the mitral valve is shown. **Solid arrow** in **a** points to the apex of the cleft. Accessory chordae extend from the anterior margin (**broken arrow**) and from the posterior margin (**open arrow**) of the cleft to the margins of the deficient ventricular septum. The "scooped out" appearance of the muscular septum is similar to that seen in classic endocardial cushion defect. The summit of the ventricular septum is closed by a membrane which was judged to be tissue of the tricuspid valve. LA = left atrium; other abbreviations as in Figure 3.

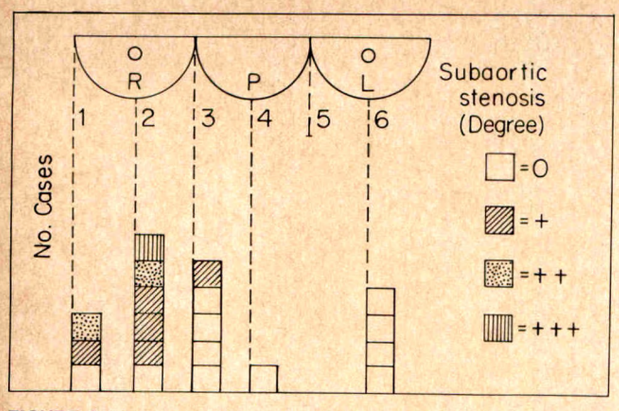

FIGURE 8. Various positions of ectopic chordal insertion as defined in Figure 2, according to the degree of subaortic stenosis. 0 = no subaortic stenosis; + = mild, ++ = moderate, and +++ = severe subaortic stenosis, respectively. The case with l-transposition of the great arteries is not included.

also present. In the 1 case with aortic atresia, septal attachment of accessory chordae of the cleft mitral valve caused subaortic obstruction, in addition.

Functional Consequences

As stated, the principal basis for interpreting functional effects of the anomaly of the mitral valve was the appearance of the specimen. The 2 major consequences of the cleft in the anterior mitral valve appeared to be mitral insufficiency and subaortic stenosis. The principal factors favoring an opinion that mitral insufficiency had been present were left atrial enlargement, right ventricular hypertrophy, and, to some extent, left ventricular enlargement.

Subaortic stenosis was judged to have been present when associated anomalous attachment of the anterior leaflet of the mitral valve to either the ventricular septum or anterior wall of the right ventricle had restricted significant movement of the anterior mitral leaflet from the septal wall of the left ventricle.

Mitral insufficiency: In each of the 9 cases in which the mitral cleft was the only significant anomaly (Group I), some degree of mitral insufficiency was considered to have been present. Three of the patients died from congestive cardiac failure. This functional disturbance was more difficult to evaluate in those cases having significant anomalies in addition to the mitral cleft. Nevertheless, among the 11 cases with additional anomalies, mitral insufficiency had either been demonstrated clinically or interpreted from the specimen as having been present in 6 cases (3 moderate and 3 mild). Among the remaining 5 cases with additional anomalies, mitral insufficiency was considered not to have been present in each, including the 1 case of corrected transposition and right-sided mitral valve. In the latter case, ventriculography had demonstrated competence of the valve.

Correlations were attempted between the presence or absence of mitral insufficiency and, when present, its degree on one hand, and certain features of the mitral valve on the other (Fig. 9). These were: (1) dimension of the cleft, (2) the width of the base of the anterior leaflet compared with the width of the base of the posterior leaflet, (3) the position of the cleft, and (4) the presence of ectopic chordae.

Ratios were determined of the width of the cleft compared with the width of the base of the anterior leaflet. These ranged from 0.1 to 0.5.

The wider the cleft, the more likely was the presence of mitral insufficiency. With this ratio, a statistically significant difference ($p < 0.025$) was found between subjects with absent or mild mitral insufficiency on one hand, and subjects with moderate or severe mitral insufficiency on the other (Fig. 10).

Ratios were determined for the depth of the cleft compared with the depth of the anterior mitral leaflet. There was no relation between these values and mitral insufficiency.

Ratios were obtained of the width of the entire mitral anulus to the width of the base of the anterior mitral leaflet. These ranged from 1.6 to 2.4. No relation between these ratios and mitral insufficiency was noted.

The position of the cleft was not always central in the anterior leaflet as judged by the fact that the anterior and posterior halves of the leaflet were not always equal. Mitral regurgitation was always found when the anterior portion of the cleft leaflet was larger than the posterior.

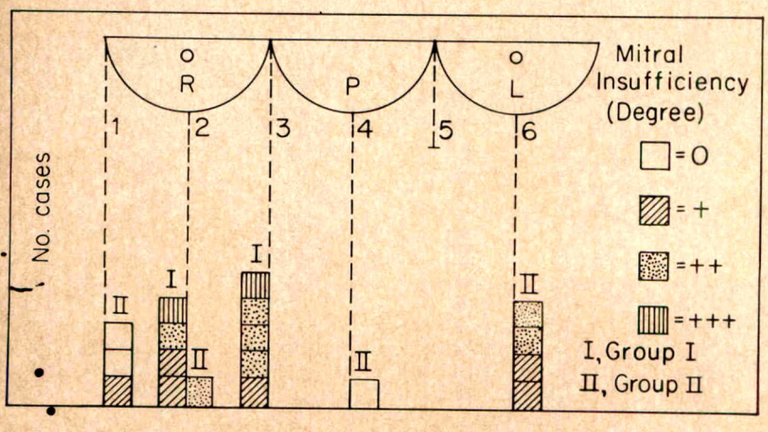

FIGURE 9. Various positions of ectopic chordal insertion as defined in Figure 2, according to the degree of mitral insufficiency. 0 = no mitral insufficiency; + = mild, ++ = moderate, and +++ = severe mitral insufficiency, respectively. The case with l-transposition of the great arteries and a case in which evaluation of mitral insufficiency was not possible are not included.

Symmetrically cleft leaflets or leaflets with a larger posterior component varied as to the presence of mitral insufficiency.

There was no obvious correlation between the site of insertion of accessory chordae on one hand, and mitral insufficiency on the other. This lack of correlation may result from the fact that the presence of the cleft is the primary determinant of mitral insufficiency. Nevertheless, some influence of chordal insertion may have played a role in favoring mitral insufficiency. For example, in Case 3 as shown in Figure 6, a small cleft with anterior insertion of ectopic chordae beneath the commissure between the right and posterior aortic cusps was associated with severe mitral insufficiency.

Left ventricular outflow stenosis: From pathologic examination, narrowing of the left ventricular outflow tract was considered to have been present in 10 cases. This abnormality, among the most severe forms of subaortic stenosis, had been diagnosed clinically in some. Based on our interpretation of the presence or absence of subaortic stenosis, in both Groups I and IIA, left ventricular outflow tract stenosis was determined to be clearly related to the site of septal insertion of accessory chordae, namely into the ventricular septum beneath the right aortic cusp (Fig. 8). In 3 cases, relatively long accessory chordae appeared to have caused a degree of subaortic stenosis which was less than that expected from the position of their septal insertion. In cases with d-transposition of the great arteries (IIB), left ventricular outflow stenosis was rare. In the case with l-transposition of the great arteries (IIC), the narrowing of the outflow tract of the right-sided morphologic left ventricle was caused by accessory tissue of the mitral valve and not by the insertion of accessory chordae.

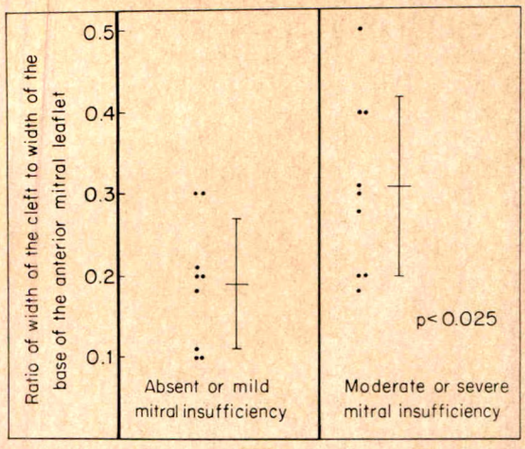

FIGURE 10. Correlation between the ratio of width of the cleft to width of the base of the anterior mitral leaflet and the degree of mitral insufficiency. In subjects with absent or mild mitral insufficiency, the ratio was 0.19 ± 0.8 (standard deviation) and in subjects with moderate or severe mitral insufficiency, the ratio was 0.31 ± 0.12 ($p < 0.025$). Two of the cases in the study are not represented.

Discussion

The anomaly described in this communication consists of a cleft of the anterior mitral leaflet. The cleft may involve a variable length on the anterior mitral leaflet and is usually shaped like an inverted V. As a result of the cleft, the anterior mitral leaflet is divided in anterior and posterior components. Accessory tissue taking the form of chordae, a raphe structure, or both extends from the ventricular aspect of the intact portion of the cleft leaflet to the ventricular septum or the anterior wall of the left ventricle. The latter process may cause left ventricular outflow tract stenosis.

The question might be raised as to whether the cleft is acquired or congenital. Acquired disease giving rise to a defect would, of necessity, be a destructive inflammatory process such as bacterial endocarditis. Militating against this possible cause is the fact that no torn chordae were seen in any of the hearts examined. An important factor favoring a congenital origin is the presence of accessory tissue that attaches to the cleft, either at its apex or along the tissue edging the cleft.

The cleft is of the same type as seen in classic examples of persistent common atrioventricular canal or endocardial cushion defect.[1,4] Thus, the condition of cleft anterior mitral leaflet may be considered a forme fruste of the endocardial cushion defect in which the septal defects that characterize the full picture of the malformation are absent. Additional features related to the endocardial cushion defect may be found in hearts with a cleft in the anterior mitral leaflet. These include abnormally increased ratio of length of left ventricular outflow to inflow tract, "scooped out" deficiency of the ventricular septal summit, cleft of the septal tricuspid leaflet, and double mitral orifice. The association with Down's syndrome in 4 of our 20 cases, a condition frequently associated with the endocardial cushion defect, further stresses the embryologic relation of the isolated cleft mitral valve with endocardial cushion defect.

As far as we are aware, isolated cleft of the mitral valve was first described by one of us (JEE) in 1954.[1] A few reports of examples of this condition have since been reported. We were able to find only 36 cases,[1–21] 9 of which correspond to 9 of our 20 cases.[1,4,10,16–19] Eleven of our cases have not previously been reported. Associated cardiac anomalies were found in 27 of the 36 reported cases to which reference has been made.[4–16,18–21] The most frequent of such anomalies was a fossa ovalis (secundum)-type atrial septal defect (15 cases).[4–9,11–14,20] The unusual association of a secundum-type atrial septal defect with a cleft mitral valve was the source of diagnostic errors, since this defect of the mitral valve is classically associated with an ostium primum atrial septal defect. Other associated anomalies reported were transposition of great arteries,[16–18] tricuspid atresia,[18] pouches of the tricuspid valve,[19] left ventricular-right atrial communication,[19] coarctation of aorta,[7] ventricular septal defect,[7–14] partial anomalous pulmonary venous connection,[15] and double-outlet right ventricle.[21] The tendency of a cleft of the anterior mitral leaflet to be associated with other cardiac malformations is emphasized by the present series.

The scarcity of the reported cases appears to be due to the rarity of the syndrome, as well as to difficulty of the clinical differentiation from other causes of mitral

insufficiency and subaortic stenosis. Most of the reported cases were correctly recognized at operation or at autopsy. The diagnostic value of the electrovectorcardiogram was suggested in the past.[5,6,12,13] A left-axis deviation with counterclockwise rotation of the initial vector on the frontal plane, such as that seen in atrioventricular canal defect,[25,26] was considered a useful sign of mitral valve cleft; but, judging from limited electrocardiographic data in our material, this sign is infrequent in our series.

Angiographic diagnosis of the mitral valve cleft is usually possible in atrioventricular canal defect. However, as far as the isolated mitral valve cleft is concerned, the angiographic demonstration of the cleft was unsuccessful according to the experience of others and in the cases in our material.[7,11–13,15,16] The usefulness of angiography lies in its ability to quantify the mitral insufficiency rather than in its ability to identify its cause.

It has been recently shown that the mitral valve cleft can be precisely imaged by 2-dimensional echocardiography.[22] The finding of a cleft mitral valve is a cardinal echocardiographic sign of atrioventricular canal defect. The echocardiographic diagnosis of cleft of the anterior mitral leaflet in 2 cases associated with double-outlet right ventricle has been reported.[21] We have personal experience with 2 living patients having severe mitral insufficiency and no septal defects as shown by cardiac catheterization whose echocardiograms showed a typical mitral valve cleft and intact atrial and ventricular septa.

Various degrees of left ventricular outflow tract stenosis were interpreted as having been present in about half of our cases.

The condition appears to result from restraint of the anterior mitral leaflet by accessory chordae that attach to the ventricular septum. This phenomenon was described by Sellers et al[17] in 1964. Our cases emphasize the point that cleft mitral valve may simultaneously cause subaortic stenosis and mitral insufficiency. In this way the anomaly described herein must be distinguished from hypertrophic muscular subaortic stenosis.

While the condition represents a "minor" lesion from the embryologic point of view compared with the usual picture of the endocardial cushion defect, in many cases it represents a severe clinical disease which requires surgery early in childhood. The problem of mitral valve surgery in children is obviously avoiding replacement of the valve. Plastic repair of the affected leaflet has been reported in 18 cases of isolated mitral valve cleft.[2,5–8,11–15,20] In the majority of these cases, the results of operation were evidently successful. This experience on a limited number of cases matches the larger experience of repair of cleft valves of atrioventricular canal defects.[27] The rationale for reparative surgery seems well based. Our data show that potentially correctable factors causing mitral insufficiency may be identified. These factors are the width of the cleft and perhaps the septal insertion of ectopic chordae. In the past, the role of these elements was recognized in the cleft mitral valve of persistent common atrioventricular canal.[28] Suture of the cleft and resection of the accessory chordae are probably both necessary for a complete correction of the altered function of the mitral valve.

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Isolated Cleft Mitral Valve: A Variety of Congenital Mitral Regurgitation Identified by 2-Dimensional Echocardiography

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Nine children with isolated cleft mitral valve, aged 1 day to 12 years, were studied. The electrocardiogram showed a normal QRS axis in 5 subjects. Cardiac catheterization was performed in 4 patients and demonstrated severe mitral insufficiency in 3 but failed to clearly demonstrate a cleft mitral valve or gooseneck deformity. The mitral cleft was confirmed at operation in 2 patients.

Two-dimensional echocardiography demonstrated a cleft dividing the anterior mitral leaflet into 2 portions in each patient. The mitral anulus was normally positioned and the atrioventricular septum present. Atrial and ventricular septa were intact. Features similar to anatomic studies such as accessory chordae and thickening of the edges of the cleft with increasing age were also seen. Two-dimensional echocardiography is the only method available to reliably diagnose isolated cleft of the mitral valve.

Cleft anterior leaflet of the mitral valve is usually associated with atrial or ventricular septal defects of persistent atrioventricular canal (endocardial cushion defect) type. As an isolated anomaly, cleft mitral valve is a rare cause of mitral regurgitation (MR).[1-11] The clinical and angiographic differentiation of this condition from other causes of MR is difficult. Most reported cases have been diagnosed at operation or at autopsy. Two-dimensional (2-D) echocardiography precisely images the anatomy of the mitral valve, and findings of cleft mitral valve associated with other forms of endocardial cushion defect have been described.[12,13] We identified 9 children with cleft mitral valve and intact atrial and ventricular septa using 2-D echocardiography. This study reports the echocardiographic, clinical, and hemodynamic findings in these patients.

Methods

Nine patients, 6 female and 3 male, aged 1 day to 12 years, were studied (Table I). Twelve-lead electrocardiograms and thoracic roentgenograms were obtained in all patients. Cardiac catheterization was performed in 4 patients (Table II). MR was graded on a scale from 1+ to 4+ by cine left ventriculography.[14] In 2 patients (Cases 2 and 3), the diagnosis was confirmed at operation.

Two-dimensional echocardiograms were performed with a Smith Kline Instruments mechanical sector scanner using a 30° or 80° 5 MHz transducer or with an Advanced Technology Laboratories mechanical sector scanner using an 80° 5 MHz transducer. In each patient, standard parasternal, subcostal, and apical views were obtained and recorded on video tape.

Results

One patient (Case 9) had 3 siblings with partial atrioventricular canal defect. Seven patients were asymptomatic including 3 infants, 1 of whom had trisomy 21 (Case 6). A 6-year-old girl (Case 2) had severe exercise intolerance and orthopnea. A 12-year-old boy (Case 4) complained of decreased exercise tolerance after age 6. The first and second heart sounds were normal in all patients. An apical pansystolic murmur (grade 2/6 to 4/6) radiating to the axilla and the back was heard in all patients. A third heart sound was heard in 4 subjects; in 3, it preceded a mid-diastolic rumbling murmur. Electrocardiograms showed a prolonged P-R interval in 3 patients (Table I). The QRS axis was normal in 5 patients, and in the remaining 2 patients it was 0° to −120°. Signs of left atrial enlargement and left ventricular hypertrophy were present in 2 patients. One patient had electrocardiographic evidence of biventricular hypertrophy. Thoracic roentgenograms showed an enlarged left atrium in 4 patients, left ventricular enlargement in 3 and pulmonary venous congestion in 2. Five patients had normal findings on roentgenography.

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TABLE I Electrocardiographic Data

Case	Sex	Age	P-R Interval (seconds)	QRS Axis	Left Atrial Enlargement	Left Ventricular Hypertrophy	Right Ventricular Hypertrophy
1	F	5 years	0.14	−110°	0	0	0
2	F	6 years	0.12	+90°	+	+	+
3	F	11 years	0.21	+28°	0	0	0
4	M	12 years	0.18	+58°	+	+	0
5	F	1 day	0.08	0°	0	0	0
6	F	1 day	0.12	−120°	0	0	0
7	F	10 days	0.10	+180°	0	0	0
8	M	4 years	0.14	−20°	0	0	0
9	M	11 years	0.18	+60°	0	0	0

+ = present; 0 = absent.

Cardiac catheterization (Table II) was performed in 4 patients. Three patients had a clinical diagnosis of MR and radiographic evidence of cardiomegaly; 2 of these were symptomatic. The fourth patient was initially referred for cardiac catheterization with a clinical diagnosis of complete atrioventricular canal defect, with a normal thoracic roentoenogram and no symptoms. No oximetry or angiographic evidence of an intracardiac left-to-right shunt was found in any patient. Pulmonary arterial wedge pressure was increased in 2 patients. A 10 mm Hg peak systolic pressure difference between the left ventricle and the aorta was found in 1 patient (Case 4).

At cine left ventriculography, severe MR was found in 3 patients (Cases 2, 3, and 4); in 2 (Cases 2 and 4), prolapse of a portion of the mitral valve was present. The fourth patient (Case 1) had no MR, but radiolucent structures were identified in the left ventricular outflow tract during systole. These structures were interpreted as representing accessory mitral valve tissue. No patient had a gooseneck deformity or a clearly seen cleft of the mitral valve anterior leaflet. The atrial and ventricular septa were intact in all 4 patients.

Surgery was performed in 2 patients (Cases 2 and 3). In Patient 2, the cleft in the anterior leaflet extended to the anulus and divided the leaflet into 2 unequal parts (Fig. 1). This cleft was easily closed with interrupted sutures resulting in a pliable leaflet that guarded two thirds of the mitral orifice and created no stenosis. The scallops of the posterior leaflet were small, thickened, had rolled edges, and moderate prolapse. These scallops did not coapt with the anterior leaflet. The resultant MR was deemed excessive and therefore the mitral valve was resected and replaced with a Björk-Shiley prosthesis. The patient had an uneventful recovery. Her exercise tolerance improved and cardiac size seen in the thoracic roentgenograms was significantly reduced. Surgical findings in Patient 3 were similar, although the rolling and thickening of mitral valve tissue was less marked. Suture closure of the mitral cleft resulted in a competent mitral valve.

With the exception of accessory mitral valve tissue in Patient 1, the echocardiographic appearance of the mitral valve was similar in all 9 patients, and will be discussed together. In these patients, the mitral valve was well seen in the standard short-axis orientation, rather than the more vertical short-axis plane which has been suggested for demonstrating the mitral cleft in endocardial cushion defect.[13] The parasternal short-axis view demonstrated the cleft anterior mitral leaflet better than the subcostal short-axis view in 8 patients. In 1 newborn infant the cleft leaflet was better seen on subcostal images. During diastole, the anterior mitral leaflet separated widely into medial and lateral portions in all patients (Fig. 2). In 7 patients, the anterior edges of the cleft mitral leaflet apposed the ventricular septum. The portions of the anterior leaflet were similar in width in 4 patients. In the other 5, the lateral portion of the leaflet was wider than the medial (Fig. 2). The anterior leaflet appeared normal in thickness in all patients. However, the edges of the cleft appeared thickened and rolled toward the left ventricle in all patients except the 3 infants (Cases 5, 6, and 7).

In systole the anterior mitral leaflet formed a continuous echo in 8 patients. In 1 patient (Case 3) a gap of about 2 mm between the 2 portions of the anterior

TABLE II Cardiac Catheterization Data

		Pressures (mm Hg)								
		Right Atrium		Pulmonary Artery		Pulmonary Artery Wedge	Left Ventricle	Aorta		
Case	Superior Vena Cava O_2 (%)	Mean	O_2 (%)	S/D	O_2 (%)	(Mean)	S/D	S/D	O_2 (%)	Mitral Regurgitation
1	69	2	72	22/9	71	13	100/13	98/58	97	0
2	67	5	67	58/28	66	20	90/15	90/55	96	4+
3	78	5	74	22/12	74	12	93/10	95/68	97	4+
4	73	5	75	28/16	73	17	115/13	105/65	97	3+

Mitral regurgitation: 0 = absent, 3+ or 4+ = degree of regurgitation; O_2 (%) = percent oxygen saturation; S/D = peak systolic/end-diastolic.

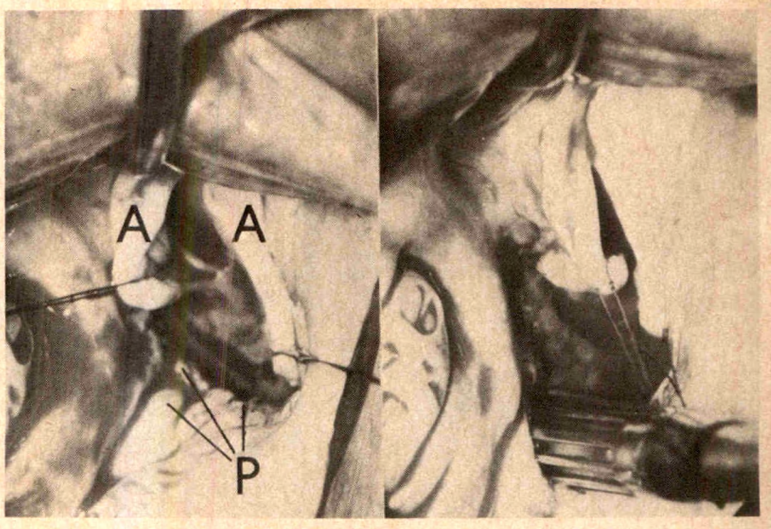

FIGURE 1. Case 2. Mitral valve viewed from above at the time of operation. **Left,** a cleft divides the anterior leaflet into similar segments (A). The scallops of the posterior leaflet of the mitral valve (P) are thickened, have rolled edges, and are small. **Right,** the 2 components of the cleft mitral valve are pulled together by the stay sutures. The cleft is complete to the level of the anulus. There is adequate anterior leaflet tissue for repair. The repaired anterior leaflet guarded approximately two thirds of the mitral valve orifice.

leaflet persisted in systole. Two patients (Cases 2 and 4) had a mild degree of mitral valve prolapse.

Linear echoes extending from the coaptation line of the cleft anterior leaflet to the upper portion of ventricular septum (Fig. 3) were seen in 3 subjects (Cases 2, 4, and 6). These echoes probably represent accessory chordal attachments from the mitral valve to the ventricular septum as have been noted in autopsy studies.[17] The 3 patients with echocardiographic evidence of accessory chordae tendineae also had systolic anterior bending of the basal portion of the anterior leaflet. This was interpreted as resulting from restraint of motion of the anterior mitral leaflet by the accessory chordae. As a result of the presence of accessory chordae and of the systolic anterior bending of the mitral valve, the left ventricular outflow tract appeared narrow on the echocardiograms of all 3 patients (Fig. 3). However, this was not associated with significant hemodynamic abnormalities in the 2 patients in whom cardiac catheterization was performed.

Atrial and ventricular septal defects were not detected with echocardiography in any patient. Mitral and tricuspid valve anuli were at different levels in all patients (Fig. 4). Thus, the atrioventricular septum (shared by the left ventricle and right atrium), which is between the anuli of the atrioventricular valves, was demonstrated in all subjects.

Two patients had echocardiographic abnormalities besides those involving the mitral valve. In one (Case 1), multiple echoreflective structures that protruded into the left ventricular outflow tract during systole and appeared to be attached to the mitral valve apparatus were recorded. These corresponded to angiographic findings suggesting accessory mitral valve tissue. In the other patient (Case 7), multiple echoes were recorded from the aortic valve which domed during systole,

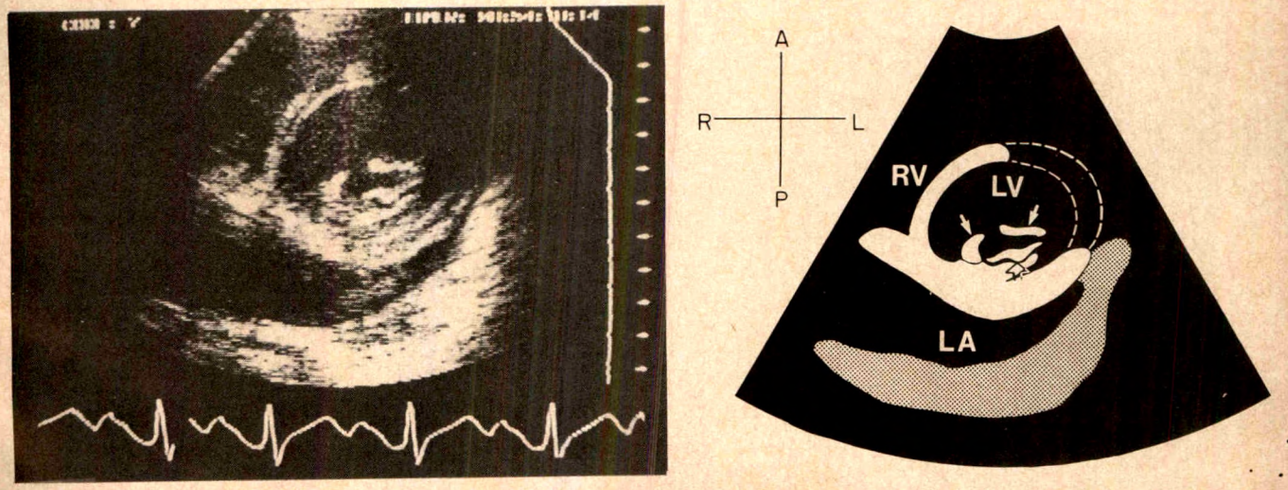

FIGURE 2. Case 2. Two-dimensional echocardiogram in the parasternal short-axis view, and corresponding schematic drawing. A cleft divides the anterior mitral leaflet into 2 portions of different size (**solid arrows**). The posterior mitral leafet (**open arrow**) is behind the cleft anterior leaflet. The echo-free space behind the left ventricle (LV) is an extension of the markedly enlarged left atrium (LA). A = anterior; L = left; P = posterior; R = right; RV = right ventricle.

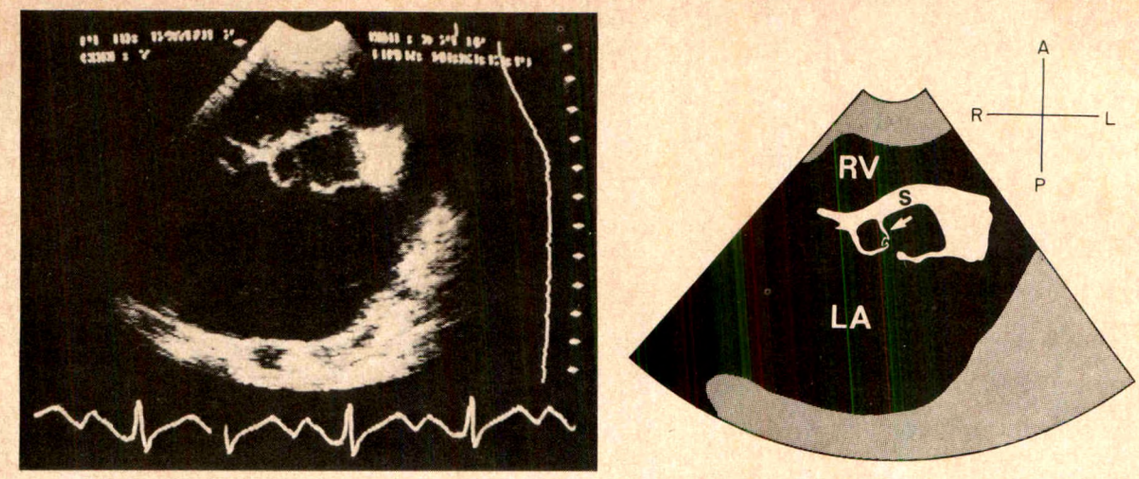

FIGURE 3. Case 2. Two-dimensional echocardiogram in the parasternal short-axis view and corresponding schematic drawing. A thin linear echo representing an accessory chorda (**arrow**) extends from the coaptation point of the halves of the anterior mitral leaflet to the upper portion of the interventricular septum (S). Mild narrowing of the left ventricular outflow tract results from the presence of the accessory chorda. Abbreviations as in Figure 2.

suggesting an abnormal aortic valve. This patient also had an apical systolic ejection click.

Discussion

The anatomic aspects of cleft mitral valve without septal defects of the endocardial cushion defect type (so-called isolated cleft of the mitral valve) have been recently reviewed in a study of 20 hearts.[15] In this anatomic study, the mitral anulus was normally located. The cleft extended for a variable depth on the anterior mitral leaflet except at its base, where the leaflet was undivided. The cleft divided the anterior leaflet into 2 equal portions in 8 specimens, whereas in the others the medial and lateral portions of the anterior leaflet were of different widths. The mitral leaflet was normally thin and smooth in patients younger than 2 years of age. In patients older than 4 years of age, the edges of the cleft were thickened by fibrous tissue in all cases. Accessory chordae tendineae extended from the apex of the cleft or, rarely, from the edges of the cleft to the ventricular septum or anterior wall of the left ventricle.

These anatomic features of isolated cleft mitral valve were demonstrated by 2-D echocardiography in the 9 patients we studied. The normal position of the mitral valve anulus was confirmed by the absence of a deficiency (so called scooping out) of the crest of the ventricular septum. In no patient were the mitral and tricuspid valve anuli at the same level on the crest of the ventricular septum. In contrast, the atrioventricular septum, characteristically absent in ostium primum defect with or without associated ventricular septal defect[16] was demonstrated in each of our patients. Moreover, the mitral valve was well seen in the usual short-axis plane. This is in contrast to the vertical or-

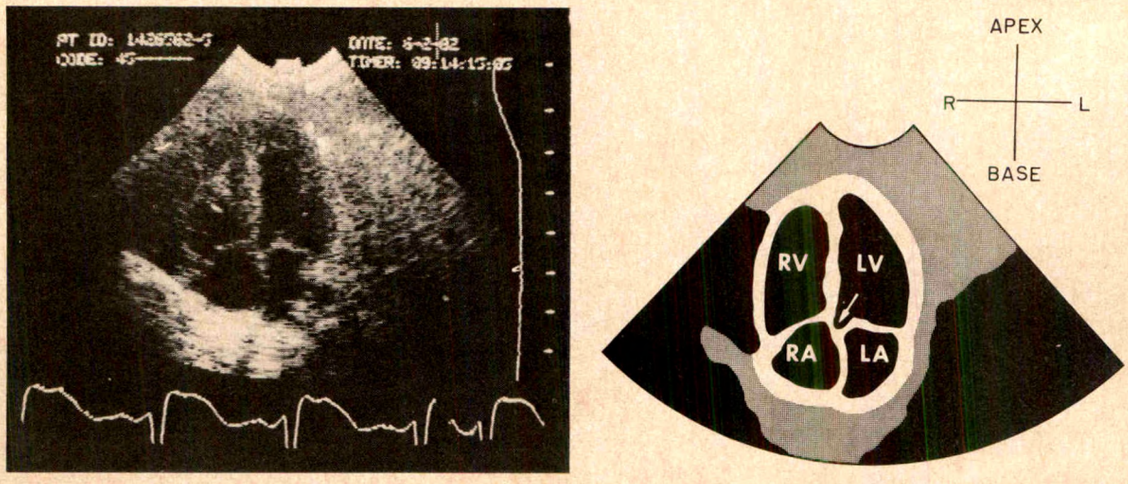

FIGURE 4. Case 6. Two-dimensional echocardiogram in the apical 4-chamber view and corresponding schematic drawing. The atrial septum and the ventricular septum are intact. The atrioventricular septum (**arrow**) is between the mitral and tricuspid annuli. RA = right atrium; other abbreviations as in Figure 2.

ientation of the echocardiographic cross section required for optimal visualization of the cleft mitral leaflet in other forms of endocardial cushion defect.[13] In isolated mitral cleft, the mitral anulus is in a normal position and the cleft points toward the left ventricular outflow tract; in other forms of persistent atrioventricular canal, the mitral anulus is vertically oriented and the cleft points toward the ventricular septum.[17] The basal portion of the anterior leaflet appeared intact in the echocardiogram in all instances. The relative widths of the portions of the cleft leaflet were easily recognized. The age distribution of the echocardiographic appearance of thickening and rolling of the edges of the cleft paralleled that of the anatomic study.[15] Only in the 3 infants (Cases 5, 6, and 7) did the edges of the cleft appear thin. Moreover, in 3 patients accessory chordae tendineae were demonstrated.

To confidently make an echocardiographic diagnosis of isolated cleft of the mitral valve, one must exclude associated septal defects of the endocardial cushion defect type. The sensitivity of 2-D echocardiography in detecting septal defects of the endocardial cushion defect type is high. In the series described by Hagler et al,[12] ostium primum atrial septal defect was detected with 2-D echocardiography in each of 42 cases and ventricular septal defect in 27 of 28 cases. None of the 9 patients we examined had echocardiographic evidence of septal defects. This is supported by the absence of clinical or roentgenographic findings of a left-to-right shunt. Oximetric and angiographic documentation of intact atrial and ventricular septa were obtained in 4 cases, and confirmed at surgery in 2.

Before echocardiography was available, the clinical diagnosis of this entity was extremely difficult. Most patients reported on were diagnosed only at operation or autopsy. It has been stated that in patients with MR or even ostium secundum atrial septal defect, the finding of electrocardiographic left-axis deviation might suggest the diagnosis of cleft mitral valve.[11] However, of reported cases of isolated cleft mitral valve, left axis deviation was found only in 33%.[1,2,4,6,7,9–11] Five of our 9 patients had a normal QRS axis.

Angiographic demonstration of isolated mitral cleft was usually unsuccessful in reported cases. In the 4 patients we examined with angiography, demonstration of the cleft was questionable, and there was no evidence of the gooseneck deformity classic of other forms of endocardial cushion defect. Two-dimensional echocardiography is extremely sensitive in demonstrating the cleft of the mitral valve anterior leaflet when it is associated with a primum atrial septal defect.[12,13] When corrected transposition is not present, this echocardiographic appearance is always associated with a cleft of the mitral valve.

Two-dimensional echocardiography has the specific capacity to differentiate cleft mitral valve from other causes of MR. The importance of this echocardiographic diagnosis is heightened by the relative insensitivity of electrocardiography and angiography. Two-dimensional echocardiography may, therefore, be of help in identifying a subgroup of patients with congenital MR in whom repair of the mitral valve may be feasible without replacement.[17] This is of great importance especially in pediatric patients in whom replacement of the mitral valve carries a substantial morbidity and mortality.[18]

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Pulmonary Atresia With and Without Ventricular Septal Defect: A Different Etiology and Pathogenesis for The Atresia in the 2 Types?

LYNN M. KUTSCHE, MD and L. H. S. VAN MIEROP, MD

In 15 of 20 hearts of neonates with pulmonary atresia and intact septum (PA-IVS) and in 4 with critical pulmonary stenosis, the pulmonary valve consisted of 3 fused cusps. One of the 11 patients with a ventricular septal defect (PA-VSD) had a well-developed pulmonary root; in 8 the pulmonary trunk arose from a dimple. Two had a bicuspid valve.

In 10 of the 20 patients with PA-IVS and in those with critical stenosis, the diameter of the pulmonary trunk was normal or larger than normal. The authors believe that this is related to flow through an initially patent pulmonary valve and, perhaps more importantly, to poststenotic dilatation. In all hearts with PA-VSD, the pulmonary trunk was very small. In the patients with PA-IVS and a normal-sized pulmonary trunk and in 3 with critical pulmonary stenosis, the morphology of the ductus arteriosus was normal, suggesting that even in the former the valve was patent before birth, allowing forward flow. In all patients with small pulmonary trunk, the ductus was long, tortuous, and originated from the aortic arch in a proximal position, suggesting that reversal of flow had occurred early in development.

The authors postulate that in patients with ventricular septal defect (VSD), the pulmonary ostium becomes atretic early in development, at or shortly after partitioning of the truncoconal part of the heart has taken place but before closure of the ventricular septum. In patients with intact ventricular septum, on the other hand, atresia very likely occurs sometime after cardiac septation has been completed. In these cases the pulmonary atresia may be due to a prenatal inflammatory process, rather than representing a true congenital malformation.

The usually small to very small size of the pulmonary trunk in patients with pulmonary atresia associated with a ventricular septal defect (PA-VSD) has rarely evoked comment, presumably because it seems logical and is to be expected that in the absence of any blood flow an artery does not develop a significant caliber. In some cases the pulmonary trunk may even be reduced to a fibrous strand. Many investigators,[1–5] however, have commented upon the unexpectedly large size of the pulmonary trunk when pulmonary atresia occurs with an intact ventricular septum (PA-IVS). This and other striking differences between cases of pulmonary atresia with and those without ventricular septal defect (VSD) we believe to be due to different antenatal hemodynamic features that may provide important clues as to the pathogenesis of pulmonary atresia in the 2 groups.

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Methods

Thirty-one hearts with pulmonary atresia and 4 with critical pulmonary stenosis from infants <1 month old were available for study. In 20 patients with pulmonary atresia and in the 4 with critical stenosis, the ventricular septum was intact; in the other 11 there was an associated VSD. Four normal hearts from full-term infants of the same age group were used as controls for the measurements. Each specimen had been fixed in the distended ("diastolic") state, as is customary in our laboratory. For this purpose a cannula is tied in the superior vena cava and, in cases in which the cardiac septum is intact, also in the left upper pulmonary vein. All other vessels entering and leaving the heart are closed by ligation or placement of an appropriate size cork. The heart is submerged in alcoholic formalin and the same fixative is run into the heart through the cannula(s) at a pressure of about 20 cm of water.

After fixation, the cardiac chambers and great arteries are opened by the creation of appropriate windows. In the present study, the diameters of the ascending aorta and the pulmonary trunk were measured midway between the aortic valve and the brachiocephalic (innominate) artery and between the pulmonary trunk and the pulmonary bifurcation, respectively. The diameter of the descending aorta was measured distal to the ductus arteriosus.

Results

In Table I are listed mean heart weights and diameters of the pulmonary trunk, ascending aorta, isthmus,

TABLE I Measurements in Normal Hearts, Hearts With Pulmonary Atresia and Intact Ventricular Septum (PA-IVS), Critical Pulmonary Stenosis and Intact Ventricular Septum (PS-IVS), and Pulmonary Atresia With Ventricular Septal Defect (PA-VSD) of Infants Aged <1 Month

	Normal (n = 4)		PA-IVS (n = 20)		PS-IVS (n = 4)		PA-VSD (n = 11)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Weight of heart (g)	22	18–31	30	21.2–38.8	35.2	28.2–41.6	23.9	18.2–34.4
Diameter (mm)								
Pulmonary trunk	8.8	8–9	6.6	2–11	10.8	10–12	3.2	1–7
Ascending aorta	8.2	8–9	10.5	9–12	10.0	10	11.0	9–13
Isthmus	6.0	5–7	7.1	6–8	8.0	8	8.0	7 & 9
Descending aorta	6.8	6–7	6.4	6–7	7.0	7	6.2	5–8
Pulmonary trunk/descending aorta	1.3		1.0		1.5		0.5	
Cross-sectional area (mm^2)								
Pulmonary trunk	61		34		92		8	
Ascending aorta	53		87		79		95	
Isthmus	28		41		50		50	
Descending aorta	36		32		39		30	
Pulmonary trunk/descending aorta	1.7		1.1		2.4		0.3	

and descending aorta, as well as the corresponding cross-sectional areas and the ratios between pulmonary trunk and descending aortic diameters.

Normal newborn hearts: The observations in the 4 normal hearts essentially agree with those reported by others.[6–9] The normal pulmonary trunk at birth is slightly larger than the ascending aorta. The ductus arteriosus is normally quite short; its long axis runs parallel to that of the aortic arch, and it joins the descending portion of the aortic arch distal to the origin of the left subclavian artery (Fig. 1). At birth the segment of aortic arch between the left subclavian artery and the ductus is narrower than the remainder of the arch and than the descending aorta, hence the name "isthmus."

Pulmonary valvular atresia or critical stenosis and intact ventricular septum: *Pulmonary valvular atresia with intact ventricular septum:* In 15 of the 20 cases, the fused pulmonary cusps were quite well developed. In 14 of these, the valve was tricuspid and had the typical triradiate appearance described by many investigators[1–4,10–14] (Fig. 2); in 1 it was quadricuspid. In the remaining 5 cases, the pulmonary trunk originated proximally from a dimple and there was no evidence of a pulmonary root.

The mean diameter of the pulmonary trunk was 75% of normal (Table I). The diameter of the ascending aorta was significantly greater than normal. That of the descending aorta, however, was within the normal range. The diameter of the isthmus was intermediate between that of the ascending and descending aorta, that is, an actual isthmus was not present. In 2 cases, the isthmus could not be measured because the aortoductal junction was at or proximal to the origin of the left subclavian artery.

The ductus arteriosus was patent in all cases. In 8 its structure was normal (Fig. 3A). In all 8 cases the pulmonary trunk diameter was ≥8 mm, well within the normal range. In 3 of these it was actually greater than normal (10, 11, and 11 mm). In 9 others, the ductus was abnormally long and had the appearance of an artery arising from, rather than joining, the aortic arch. Its point of origin was further proximal than that of the normal aortoductal junction (Fig. 3B). It diverged from

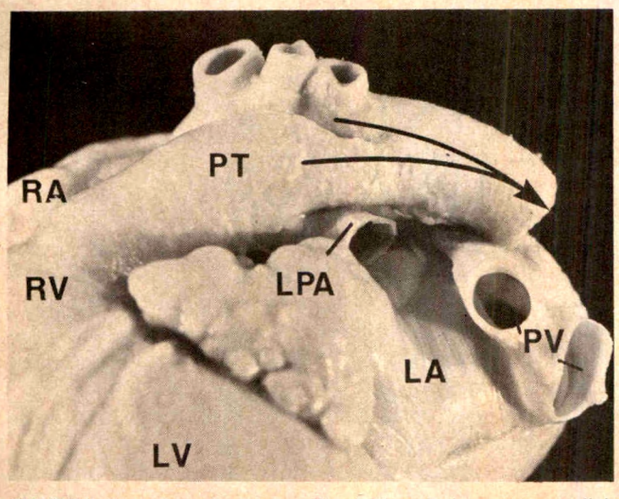

FIGURE 1. Normal newborn heart. The ductus arteriosus runs parallel to the aorta and joins the aorta at an acute angle. **Arrows** indicate direction of blood flow. LA = left atrium; LPA = left pulmonary artery; LV = left ventricle; PT = pulmonary trunk; PV = pulmonary veins; RA = right atrium; RV = right ventricle.

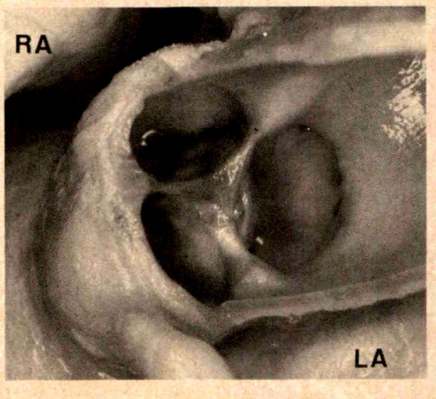

FIGURE 2. Pulmonary valve in a case of pulmonary atresia with intact ventricular septum. The sinuses of Valsalva and the valve cusps are well developed. LA = left atrium; RA = right atrium.

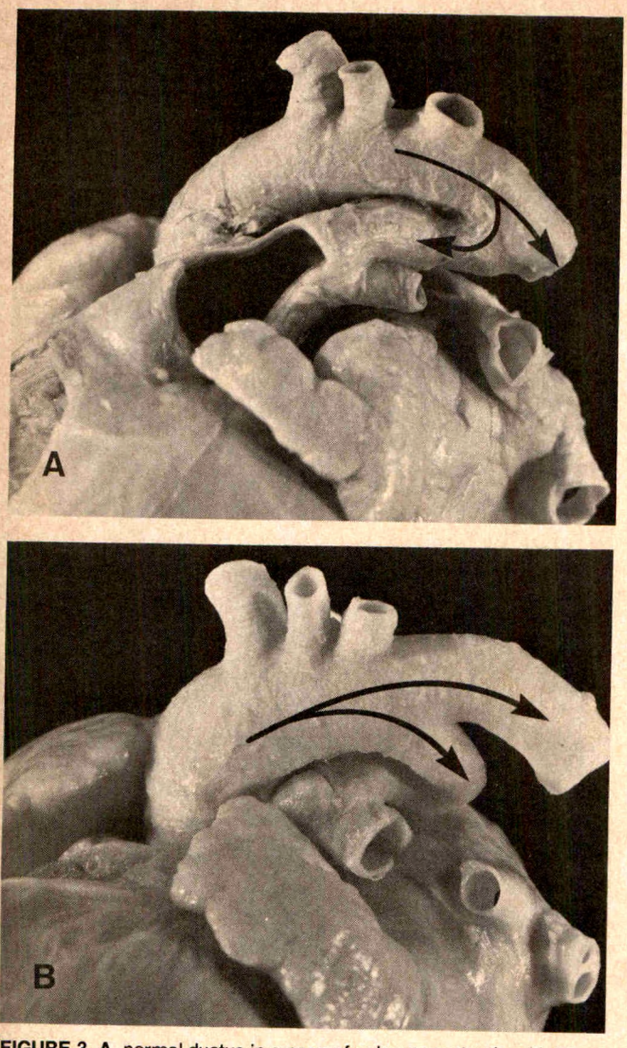

FIGURE 3. A, normal ductus in a case of pulmonary atresia with intact ventricular septum. The pulmonary trunk to descending aorta ratio was 1.5. **B,** sigmoid-shaped ductus in a case which had a pulmonary trunk to descending aorta ratio of only 0.3.

the aortic arch at an acute angle and then, turning back on itself, joined the left pulmonary artery at or near the bifurcation of the pulmonary trunk. In all these cases with a sigmoid-shaped ductus, the diameter of the pulmonary trunk was ≤6 mm. In the remaining 3 hearts, the ductus resembled the normal but joined the distal aortic arch at an angle of about 90°, that is, its structure was intermediate. The pulmonary trunk diameter in these cases was in or below the normal range.

The right ventricular cavity was small to very small ("peach-pit" right ventricle) in 4 of the 8 cases with normal ductus, in 7 of 9 with a sigmoid ductus, and in 2 of 3 with an intermediate-type ductus. In only 7 of the 20 cases was it normal or larger than normal.

Critical pulmonary valvular stenosis with intact ventricular septum: The morphology of these hearts was almost identical to that of the previous subgroup. The pulmonary valve was triradiate but had a pinpoint opening. The pulmonary trunk diameter in all 4 of our cases was greater than normal (Table I), as was the diameter of the ascending aorta. The descending aortic diameter fell within the normal range. As in PA-IVS, the diameter of the isthmus was intermediate between the ascending and descending aorta. In 1 of the 4 cases, the ductus arteriosus was sigmoid-shaped and originated from the aortic arch proximal to the left subclavian artery. In this case the right ventricle was small; in the others it was nearly normal.

Pulmonary valvular atresia with ventricular septal defect: This anomaly we consider to be a form of tetralogy of Fallot in which the pulmonary valve or ostium has become atretic. In 8 of the 11 cases, the pulmonary trunk originated proximally from a dimple; in 2 cases there was a bicuspid valve with fused cusps. Only 1 case had an essentially tricuspid valve. Two of the 11 hearts weighed <18 g and were not used for measurements of arterial diameters, only for ratios and morphologic characteristics. The mean diameter of the pulmonary trunk in the other 9 hearts was much smaller than normal, while that of the ascending aorta was abnormally large, similar to that seen in cases of PA-IVS (Table I). The diameter of the descending aorta was normal. The isthmus could be measured in only 2 cases: it was wider than the descending aorta in both. In the other 9 cases, the origin of the ductus was at or proximal to that of the left subclavian artery, or the ductus arteriosus arose from the brachiocephalic (innominate) artery on the side opposite the aortic arch, that is, there was no isthmus. The ductus was long, narrow, and sigmoid-shaped in all 11 cases. The right ventricular cavity was of normal size in all cases.

Discussion

The strikingly large size of the pulmonary trunk in many if not most cases of PA-IVS would be found even more prevalent than reported if its diameter were compared with that of the descending aorta rather than with that of the ascending aorta as is usually done[1,4,11,14]—the latter is always abnormally large whenever there is marked reduction in pulmonary blood flow due to severe pulmonary stenosis or atresia.[15]

Why then is the pulmonary trunk usually relatively large when pulmonary atresia or critical stenosis is associated with an intact ventricular septum and almost invariably small to very small when there is a ventricular septal defect?[2,3,12,16–18] Why is the atretic pulmonary valve in the former tricuspid and may be almost normally formed, while it is nearly always morphologically abnormal or merely represented by a dimple in the latter? Finally, why is the ductus arteriosus usually normal if the pulmonary trunk is large, but is long and tortuous, appearing to originate in an unusually proximal position from the aorta as a branch artery rather than joining it as a parallel vessel of equal rank, if the pulmonary trunk is small?

We agree with Santos et al[19] that these questions can be answered very satisfactorily if the prenatal hemodynamics and certain associations of anomalies are taken into consideration. The relatively large size of the pulmonary trunk in most cases of PA-IVS must mean that an anterograde, that is, normally directed flow of blood was present for much or even most of prenatal life through a patent, though stenotic (or perhaps initially

even nonstenotic) pulmonary valve. However, we believe that a second and probably more important contributing factor responsible for the reasonably large and in some cases even abnormally large size of the pulmonary trunk may be the development of poststenotic dilatation during prenatal life. All 4 of our cases of critical pulmonic stenosis had an abnormally large pulmonary trunk, even the 1 with a small right ventricle and sigmoid ductus. The large pulmonary trunk in this case is difficult to explain by a mechanism other than poststenotic dilatation, since the sigmoid-shaped ductus strongly suggests marked and early reduction of right ventricular forward flow.

The normal appearance of the ductus arteriosus in many cases we consider additional evidence that direction of blood flow once was normal and, therefore, that the pulmonary valve had been patent for some period of time before birth.[19]

On the other hand, the abnormal appearance of the ductus in other cases of severe pulmonary stenosis or atresia with intact ventricular septum and in all cases of PA-VSD indicates that the pulmonary valve became atretic early in development and that the ductus functioned as an aortic tributary which carried blood *from* the aorta to the lungs, rather than from the right ventricle and pulmonary trunk *to* the aorta, as does the normal ductus. It is long because it first runs distally, diverging from the aortic arch (a hemodynamically induced morphologic adaptation), then turns back to join the proximal left pulmonary artery. It is narrow because it only has to carry blood to the lungs (5 to 10% of combined ventricular output) rather than most of the right ventricular output (55 to 60% of combined output) as does the normal ductus.[20] This type of ductus arteriosus was present in 21 of 27 cases of pulmonary atresia with VSD reported upon by Donkers,[21] but in only 3 of 13 cases without a VSD. It was present in all 6 cases of PA-VSD reported by Santos et al,[19] but in only 1 of 8 cases in which the ventricular septum was intact. This radical departure from normal morphologic development of the distal left sixth arch again must have taken place at an early embryonic age, before histologic development had advanced to a point that would make remodeling of the vessel impossible. Among our cases of pulmonary atresia, a sigmoid-shaped ductus and a small pulmonary trunk were always associated.

We conclude that the pathogenesis of the pulmonary atresia in cases associated with a VSD probably is different from that of PA-IVS. In the former the VSD, the usually absent or abnormally formed pulmonary valve, the small pulmonary trunk, and the abnormal ductus arteriosus strongly suggest that the pulmonary atresia is part of a "true" congenital cardiac anomaly, that is, due to a fundamental derangement of cardiac development. We consider the anomaly to be a form of tetralogy of Fallot which is believed by many to be due to unequal partitioning of the trunco-conal part of the heart at the expense of the right ventricular outflow tract, the pulmonary root, and the pulmonary trunk.[22–24] The anomaly therefore manifests itself at a very early gestational age and the pulmonary valve almost certainly becomes atretic at about the same time. In PA-IVS, on the other hand, the intact ventricular septum, the near-normal appearance of the pulmonary valve, the usually large, in some cases even abnormally large, pulmonary trunk, and the often normal ductus arteriosus suggest not only that the pulmonary atresia developed at a later gestational age and at a more variable time, but that in fact it may not represent a true developmental error at all (at least not always), but may be an acquired lesion, for example, due to an intrauterine inflammatory process ("fetal endocarditis") as was suggested many years ago by Abbott,[25] and more recently by Rudolph[20] and Wagner.[26]

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Pulmonary Vein Wedge Angiography: Indications, Results, And Surgical Correlates in 25 Patients

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Pulmonary vein wedge angiography was applied to 25 patients ranging in age from 4 months to 16 years. The indications for this technique include (1) determination of the presence or absence of central (intrapericardial or mediastinal) pulmonary arteries in patients with pulmonary atresia where standard anterograde injections of contrast medium do not demonstrate these, (2) determination of the patency and caliber of a nonvisualized pulmonary artery when there is distal "occlusion" by a systemic-to-pulmonary artery anastomosis, (3) determination of the patency and caliber of a nonvisualized pulmonary artery when previous pulmonary arterial banding has led to acquired pulmonary artery atresia, and (4) determination of the presence of a mediastinal pulmonary artery in patients with so-called isolated congenital unilateral absence of a pulmonary artery. Surgical correlates to the interpretation of pulmonary vein wedge angiograms are provided in 18 patients. The present data suggest that pulmonary vein wedge angiography is a safe technique that provides considerable information about (1) the caliber of the parenchymal pulmonary arteries, (2) their sizes at the hilum of the lung, and (3) the presence or absence of a mediastinal confluence of pulmonary arteries. This technique may also complement those anatomic findings derived from anterograde injection of contrast material in patients with pulmonary atresia of a congenital or acquired nature.

The surgical management of patients whose pulmonary arteries are discontinuous from the ventricular mass depends in part on adequate visualization and quantification of the central or mediastinal pulmonary arteries.[1–11] Pulmonary vein wedge angiography has proven an effective technique in demonstrating the true mediastinal (intrapericardial) pulmonary arteries (when present) when standard anterograde injections do not suffice.[12–14] From the reports of Takamiya et al[12] and others, it is clear that pulmonary vein wedge angiography has been applied primarily to patients with pulmonary atresia and ventricular septal defects. This report extends the anatomic indications for pulmonary vein wedge angiography and provides data regarding the surgical outcome of patients who required this procedure.

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Indications

We have defined 4 conditions in which pulmonary vein wedge angiography is indicated: (1) The most common indication is the delineation of so-called central (intrapericardial or mediastinal) pulmonary arteries in those patients whose pulmonary arteries are not in perforate continuity with the ventricular mass. Before pulmonary vein wedge angiography is performed, however, ventricular angiography, aortography in the ascending and descending thoracic aorta, and selective injection of bronchial arteries or other aortopulmonary collaterals will have failed to provide visualization of the central pulmonary arteries. (2) A systemic-to-pulmonary artery surgical anastomosis has the potential to completely occlude the pulmonary artery.[15,16] The technique has been used to provide information about the patency and caliber of the nonvisualized distal pulmonary artery. (3) Pulmonary arterial banding may also occlude the pulmonary artery. This can occur when the main pulmonary artery is banded, but distal migration of the band compromises (and indeed may occlude) the origin of 1 pulmonary artery (usually the right).[17,18] Similarly, if bilateral pulmonary artery bands are applied (as for truncus arteriosus), again there is the potential for acquired unilateral absence of a distal pulmonary artery. (4) Finally, we have applied this technique to patients with so-called isolated congenital absence of 1 pulmonary artery.[19]

Technique: The pulmonary vein is probed either through a preexisting interatrial communication, by way of an intact

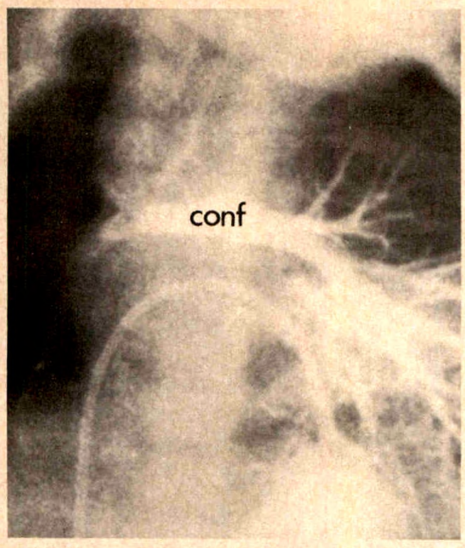

FIGURE 1. Confluent (conf) pulmonary arteries demonstrated by left pulmonary vein wedge angiography in a patient with pulmonary atresia and ventricular septal defect. Left pulmonary vein wedge injection shows confluent right and left pulmonary arteries but with an absent main pulmonary artery.

atrial septum using transseptal technique, or by using a retrograde arterial approach. When this last avenue is utilized (and assuming atrioventricular concordance), the retrograde arterial catheter is advanced to the left ventricle, through the mitral valve, and into the left atrium and pulmonary vein. An end-hole catheter is wedged in the appropriate pulmonary vein. We recommend the injection of 0.4 ml of contrast medium/kg body weight; this is injected at from 2 to 4 ml/s, with a maximal pressure of from 150 to 300 lb/in.^{2} We routinely hand-flush about 1.0 ml saline solution/kg body weight if the contrast material does not immediately reflux into the central or mediastinal pulmonary arteries. The cineangiograms are filmed at 60 frames/s. For 10 minutes before, during, and after pulmonary vein wedge angiography, the patient is given supplemental oxygen by facemask. One-cm calibration grids are routinely used at the end of the cineangiographic run to quantitate the pulmonary arteries.

Results

Twenty-five patients underwent pulmonary vein wedge angiography at the Hospital for Sick Children in Toronto from 1978 through April 1982. Nine were boys and 16 were girls. The age at pulmonary vein wedge angiography for the entire group ranged from 4 months to 16 years (median 6.95 years).

Group 1: All patients in this group had pulmonary atresia. Fifteen patients ranging in age from 4 months to 16 years (mean 6.5 ± 5.8 years; median 6.6) at the time of pulmonary vein wedge angiography comprise this group. No to 3 catheter studies had been performed before pulmonary vein wedge angiography (mean 1.06 ± 0.91). The pulmonary vein wedge injection in 14 patients was performed during the last study before consideration of surgical intervention. One patient underwent pulmonary vein wedge injections at 2 separate catheter investigations 34 months apart. The weight of these patients ranged from 5.3 to 54.6 kg (mean 19.9 ± 16.2, median 18.1).

Bilateral pulmonary vein wedge injections were performed in 4 patients; 3 patients underwent only right-sided injections and the remaining 8 patients had left-sided injections. One to 3 pulmonary veins were injected in each patient (mean 1.56 ± 0.7).

A true confluence (so-called seagull configuration) of right and left pulmonary arteries was demonstrated in 2 patients (13%) (Fig. 1 and 2), while in the remainder a confluence of mediastinal (intrapericardial) pulmonary arteries was not demonstrated. When mediastinal pulmonary arteries were not visualized, intraparenchymal pulmonary arteries were always demonstrated with extension from the hilum of the lung. At the hilum, there was considerable variation in the size of the vessels

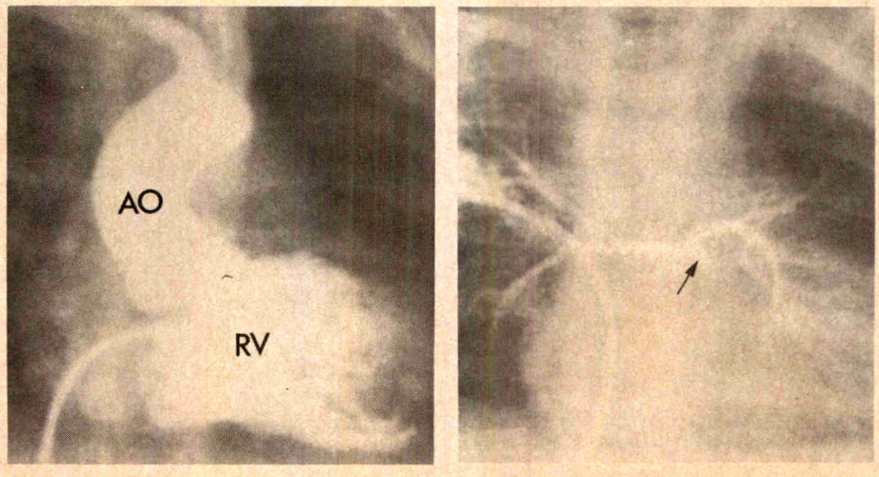

FIGURE 2. Pulmonary atresia with ventricular septal defect with confluent pulmonary arteries demonstrable only by pulmonary vein wedge angiography. **Left panel,** frontal right ventriculogram (RV) demonstrates no evidence of infundibular septation, and there is dense opacification of the ascending aorta (AO). **Right panel,** very small (2.0 mm) confluent pulmonary arteries (**arrow**) are demonstrated by pulmonary vein wedge angiography.

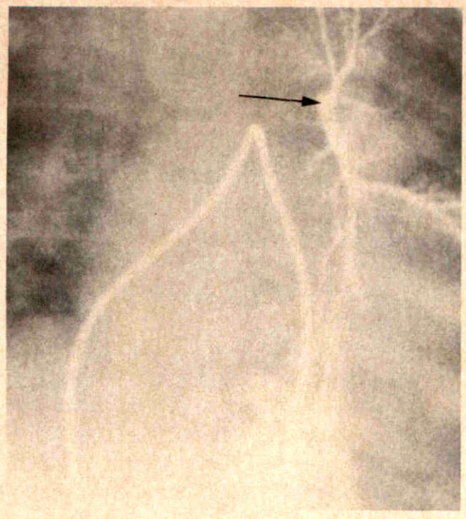

FIGURE 3. Prohibitively small hilar pulmonary artery (**arrow**) demonstrated by left pulmonary vein wedge angiography in a child with pulmonary atresia and ventricular septal defect.

(Fig. 3 to 5). From the angiographic appearance of the hilar origin of the intraparenchymal pulmonary artery, it was difficult to define with certainty the surgical accessibility. Some hilar vessels appeared to be only 2 to 3 mm in diameter (Fig. 3) while others appeared almost aneurysmal (Fig. 4). The hilar pulmonary artery (extension and confluence of intraparenchymal branches) ranged from about 2 to 15 mm in diameter.

Twelve of these 15 patients underwent heart surgery. Of the 2 with demonstrable confluence of pulmonary arteries, 1 underwent a Pott's anastomosis and the other, a right ventricular outflow tract reconstruction utilizing pericardium and leaving the ventricular septal defect open.

Ten patients with nonconfluent pulmonary arteries underwent the following surgical procedures: a Blalock-Taussig anastomosis in 7 patients (3 with Gore-tex®); right ventricular outflow tract-pulmonary artery reconstruction in 3 patients (pericardium in 2, #22 Carpentier-Edwards valved conduit in 1). Two of these 3 patients also underwent closure of their ventricular septal defects. No surgical death was encountered in these 12 patients. After the initial operation (a right Blalock-Taussig shunt), 1 patient underwent a left-sided pulmonary vein wedge injection, and a prohibitively small hilar vessel was demonstrated.

Pulmonary vein wedge angiography failed to demonstrate a confluence of mediastinal pulmonary arteries in only 1 patient where confluence (2.0 mm) was found at surgical exploration. The study had been performed early in our experience with this technique, and in retrospect, significant flushing of saline solution had not been done.

Group 2: Six patients have been identified in whom 1 pulmonary artery has been completely occluded. In 5, this was the result of a systemic-to-pulmonary artery anastomosis and in 1, a complication of a right ventricular outflow tract reconstruction. At the time of pulmonary vein wedge angiography, these patients ranged in age from 1.3 to 11.5 years. The diagnosis included the following: 1 patient with corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis; 1 with double-outlet right ventricle, hypoplastic left ventricle, acquired pulmonary atresia, infundibular ventricular septal defect, and straddling mitral valve; 3 with severe tetralogy of Fallot or pulmonary atresia with a ventricular septal defect;

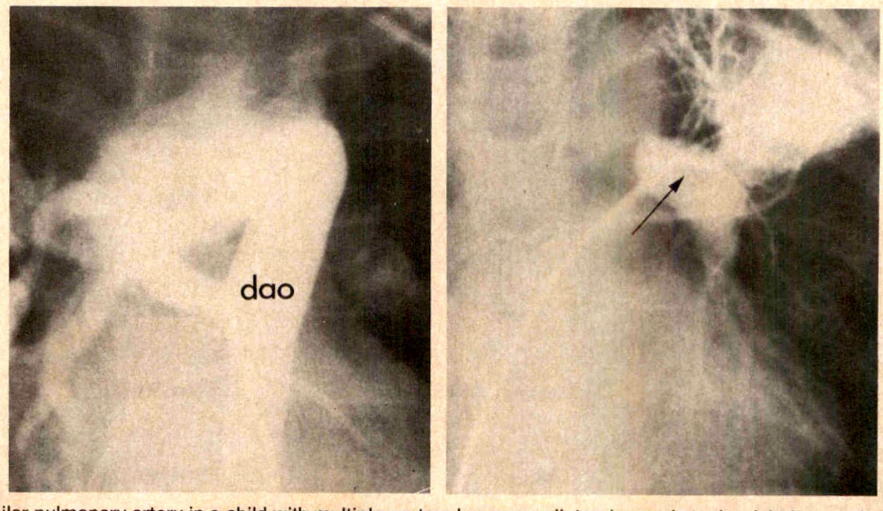

FIGURE 4. Large left hilar pulmonary artery in a child with multiple aortopulmonary collateral vessels to the right lung and presumed distal ductal (ligamental) origin of the left pulmonary artery. **Left panel,** frontal injection in descending thoracic aorta (dao) shows multiple collateral vessels to the right lung and almost none to the left lung. **Right panel,** left upper pulmonary vein wedge injection shows a hilar left pulmonary artery of about 13 mm in diameter (surgically confirmed).

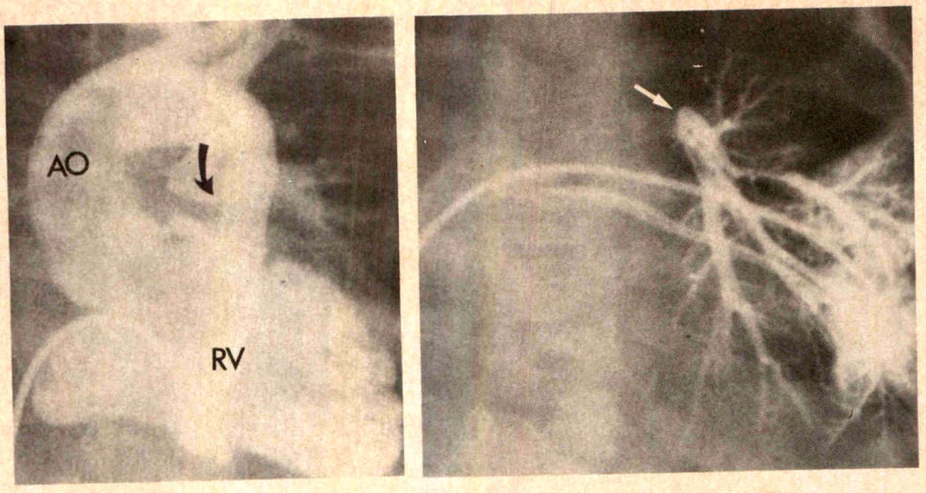

FIGURE 5. Nonconfluent pulmonary arteries originating from bilateral homologous ductus arteriosus in a patient with pulmonary atresia, ventricular septal defect, and evidence of infundibular septation. **Left panel,** the left pulmonary artery fills by way of a left ductus arteriosus (**black arrow**). **Right panel,** some months later, no opacification of the left pulmonary artery was seen from the aortogram, but a reasonable hilar left pulmonary artery (**white arrow**) was demonstrated by pulmonary vein wedge angiography.

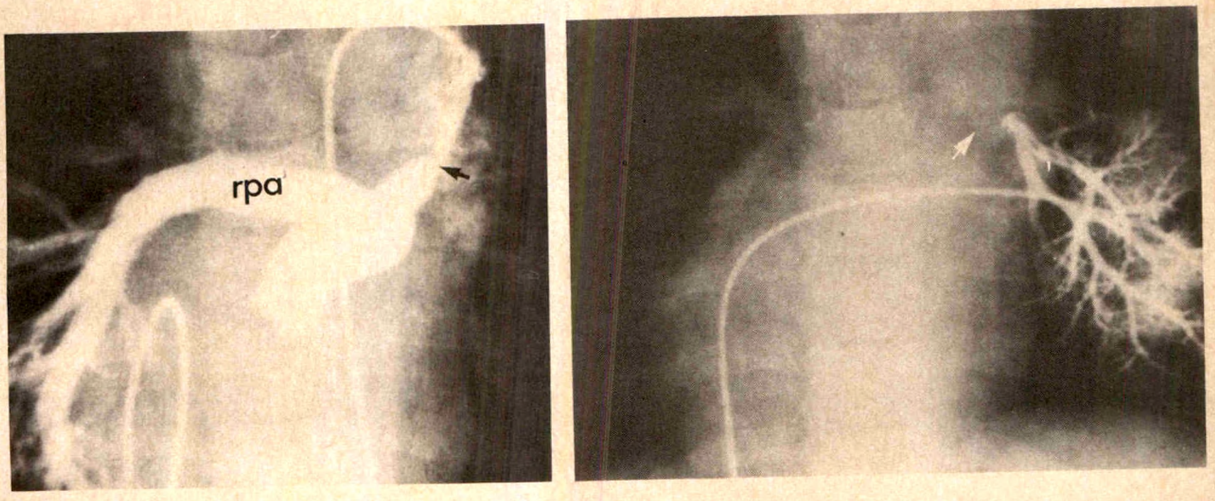

FIGURE 6. Occlusion of the left pulmonary artery by a left-sided Blalock-Taussig shunt in a patient with dextrocardia, atrioventricular discordance, single-outlet aorta, and pulmonary atresia. **Left panel,** frontal selective injection in the left-sided shunt demonstrates the caliber of the right (rpa) and main pulmonary arteries, but the left pulmonary artery distal to the shunt (**black arrow**) does not opacify. **Right panel,** a left pulmonary vein wedge angiogram demonstrates a patent but small (3.0 mm) pulmonary artery that extends to the level of the left mainstem bronchus (**white arrow**) (surgically confirmed).

and 1 patient with tricuspid atresia, restrictive ventricular septal defect, and severe pulmonary stenosis. The left pulmonary artery was the affected pulmonary artery in 5, and the right in 1 patient. The procedures responsible for complete occlusion of the left pulmonary artery included: Waterston anastomosis in 2, left Blalock-Taussig in 2, and right ventricular outflow tract reconstruction in 1. A Waterston anastomosis was responsible for complete occlusion of the right pulmonary artery in 1 patient. Left pulmonary vein wedge angiography demonstrated patency of the affected pulmonary artery distal to the occluding shunt or outflow tract reconstruction in these 5 patients, and the pulmonary artery was patent back to the level of the occluding shunt (Fig. 6). An intrapericardial right pulmonary artery was not identified by this technique. In the 1 patient whose right pulmonary artery had been obliterated by a Waterston anastomosis, only a small hilar vessel was identified.

The distal left pulmonary artery ranged from about 2 to 6 mm in diameter when visualized by pulmonary vein wedge angiography; these calibers were confirmed at the time of surgery. One patient underwent a central shunt with Gore-Tex and reconstruction of the left

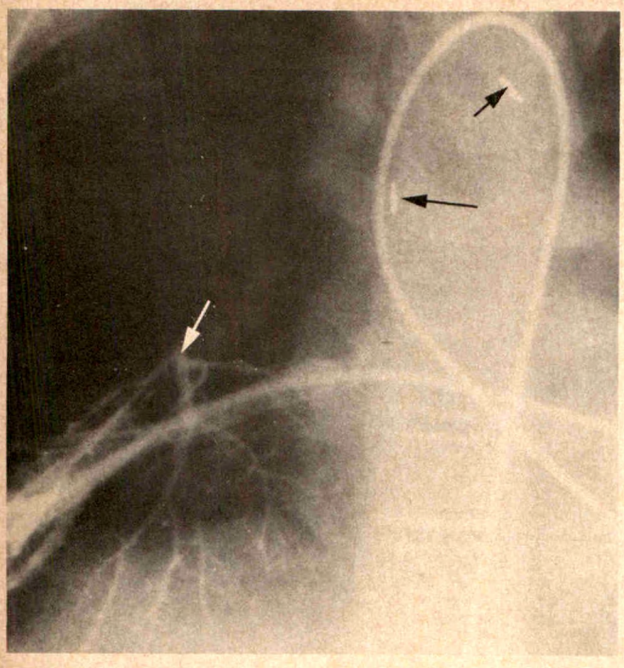

FIGURE 7. Occlusion of the distal right pulmonary artery by a right pulmonary artery band in a patient with truncus arteriosus, type 1, and bilateral pulmonary artery bands. Frontal pulmonary vein wedge injection shows a small intraparenchymal right pulmonary artery (**white arrow**). The right and left opaque pulmonary artery bands are noted (**black arrows**). See text for operative findings.

pulmonary artery. Two other patients underwent a left Blalock-Taussig anastomosis. One patient with severe tetralogy underwent a right ventricular outflow tract reconstruction with pericardium. The patch extended across the occluded origin of the left pulmonary artery. Three of the 4 patients were significantly improved by surgery.

Group 3: Pulmonary arterial banding resulted in complete occlusion (or at least nonvisualization) of the right pulmonary artery (Fig. 7) in 2 patients. One patient had had a bilateral pulmonary artery banding for a type I truncus arteriosus; the other had tricuspid atresia and transposition of the great arteries. Pulmonary vein wedge angiography was performed to determine the status of the pulmonary artery distal to the occluding band. In the patient with truncus arteriosus, pulmonary vein wedge angiography was performed by the retrograde arterial approach (Fig. 7). A mediastinal right pulmonary artery was not visualized (Fig. 7). At surgical exploration, the right pulmonary artery distal to the band was incompletely occluded with adherent thrombus extending from the level of the band to the hilum of the right lung. The pulmonary artery distal to the occluding band was shown to be patent in the second patient, but the vessel was very small. A right Blalock-Taussig anastomosis was subsequently performed.

Group 4: Two patients with so-called isolated unilateral congenital absence of a pulmonary artery have undergone pulmonary vein wedge angiography (Fig. 8). One also had a small, membranous ventricular septal defect and obstructing right ventricular anomalous muscle bundles. Pulmonary vein wedge angiography was performed in order to exclude a mediastinal pulmonary artery extending from the hilum of the affected lung to the main pulmonary artery but with atresia at its point of origin. One of these 2 patients was 3 months of age at the time of the pulmonary vein wedge injection, and the other was 4 months old. In neither was a mediastinal pulmonary artery visible (Fig. 8) and surgical exploration was not undertaken in either case.

Complications of pulmonary vein wedge angiography: Significant pulmonary complications of this technique have been uncommon.[20–22] Intrabronchial extravasation of contrast material was noted in 4 cases. One of these patients, studied early in our experience

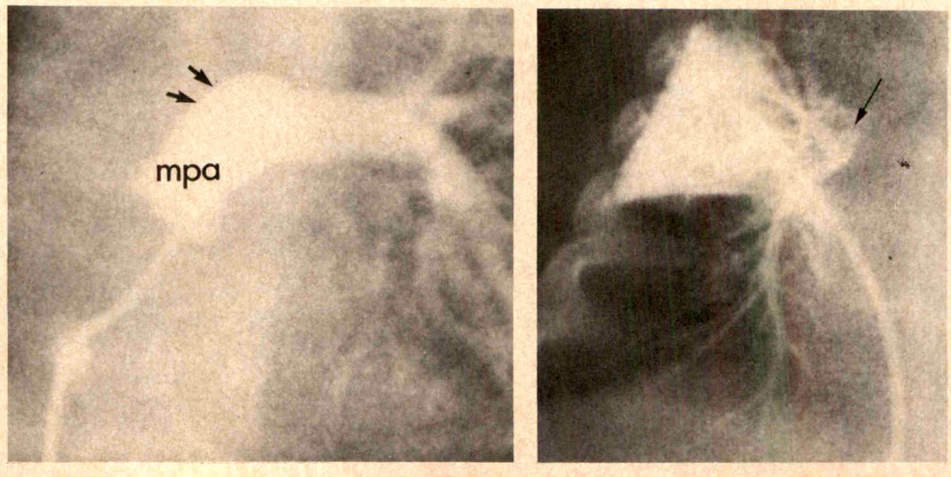

FIGURE 8. Isolated congenital absence of right pulmonary artery in a 3-month-old infant. **Left panel,** frontal main pulmonary artery (mpa) angiogram shows no filling of the proximal right pulmonary artery (**arrows**). **Right panel,** right pulmonary vein wedge angiogram shows only a small extrapericardial hilar pulmonary artery (3.0 mm). The patient did not undergo exploration.

with the technique and previously reported from this hospital, developed significant bronchospasm.[20] In the others, the extravasation produced coughing and expectoration but was well tolerated. No permanent residue was observed.

Discussion

Pulmonary vein wedge angiography has proven a relatively safe and helpful technique in our experience. Although we have extended the indications for the application of this technique, the most common indication remains the determination of the presence or absence of central pulmonary arteries in patients with pulmonary atresia, and when present, whether or not a confluence exists.

Is pulmonary vein wedge angiography really necessary when standard anterograde injections of contrast material (including selective injections of the important aortopulmonary collateral vessels) fail to visualize the central (intrapericardial or mediastinal) pulmonary arteries? In our opinion, it is. The demonstration of confluent pulmonary arteries by this technique allows a surgical alternative not permitted when a confluence does not exist. Thus, if a confluence is imaged, there is the surgical potential for connecting the right ventricle to the confluence, hopefully promoting symmetrical pulmonary blood flow and, ultimately, growth. On the other hand, if small hilar vessels only are visualized, we would still recommend surgical exploration and, when possible, construction of a systemic-pulmonary artery anastomosis into the hilum of the lung.

It must be remembered that if a lung is present, then too, the intraparenchymal pulmonary arteries are present; this is true despite the presence of pulmonary atresia. The intraparenchymal pulmonary arteries and the right and left pulmonary arteries have a different embryogenesis. For any given segment of lung in a patient with pulmonary atresia, one must determine the following: (1) How many segments of each lung connect to a true central pulmonary artery (when present)?[23] (2) Do the various segmental parenchymal pulmonary arteries interconnect? (3) What is the nature of the aortopulmonary collateral circulation, and, for any given intrapulmonary segment, what is its collateral anastomosis?[24,25] (4) Is the segment of lung protected from pulmonary vascular disease by virtue of obstruction in the aortopulmonary collateral, or at the site of connection between the aortopulmonary collateral and the parenchymal pulmonary artery?[24,26,27] Pulmonary vein wedge angiography may help resolve some of these issues, but this technique must be combined with thoughtful hemodynamic and angiographic analysis of the aortopulmonary collateral circulation.

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Familial Congenital Heart Disease: How Are The Various Types Related?

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The distribution of congenital heart lesions was studied in 238 families with at least 2 affected members. A statistical analysis was performed. Concordant lesions were found in 48% of the affected first degree relatives and in 28% of the affected second and third degree relatives. The concordance rate is highly significant for all lesions studied in the first degree relatives, with the exception of ventricular septal defect (VSD). Among the discordant pairs of lesions, some occur significantly more often than expected (tetralogy of Fallot associated with VSD, pulmonary stenosis, and transposition of the great arteries); others, such as the association between VSD and pulmonary stenosis, are significantly less common than would be expected on a random hypothesis. An explanation is proposed suggesting that malformations anatomically dissimilar but resulting from the same heart segment disorder may have some common genes, and that interaction between genes may be responsible for "antagonism" between 2 defects. The embryologic segmental approach to congenital heart disease is reinforced by this genetic study.

The incidence of congenital heart disease is higher in families with an affected member than in the general population.[1] The aim of this study is to analyze the relation between various types of congenital heart disease observed in families with at least 2 affected members.

Methods

A total of 238 families were studied; 202 had 2 affected members and 36 had more than 2. Ten of the probands were twins, 4 sets of which were certainly monozygous. Of the probands 108 were male and 130 female. The source of the family records is listed in Table I. Cases with doubtful diagnosis and cardiopathy linked to a chromosomal abnormality, known mendelian heredity, or environmental factors were excluded.

The pairs of cardiac defects observed in each family were defined as *concordant* when the 2 affected members have the same defect and *discordant* when the lesions are dissimilar. When a patient has more than 1 cardiac lesion, only what appeared to be the major lesion was considered (major lesion approach of Fraser and Hunter[2]).

Analysis of the concordance rate: For each malformation, the number of observed concordant pairs was compared with the number expected by chance. If x is taken as the frequency of this malformation among all cardiac malformations and n the number of pairs in the sample, the expected number of concordant pairs is nx^2.

Distribution of types of malformation in discordant pairs: The number of each of these pairs was compared with the number expected if this association were due only to chance. If x and y are the respective relative frequencies of malformations X and Y and m the number of analyzed pairs, the expected number of pairs "X-Y" is $mxy/\Sigma xy$. The value of the relative frequency of various types of cardiac defects was taken from Keith et al.[3]

Interpretation of test results: Because in these 2 tests the expected numbers were usually low, binomial distribution was used. Tests were always bilateral. Keeping in mind the great

TABLE I Origin of the Family Records

Hospital	Cases (n)
1. La Pitie, Paris	53
2. Henri-Mondor, Creteil	35
3. C.H.U. Nord, Marseille	24
4. C.C.M.L., Plessis Robinson	23
5. C.H.R., Nancy	22
6. Akademisch Zieckenhuis Gand	18
7. C.H.U., Rennes	12
8. Enfants-Malades, Paris	11
9. Cas Personnels, Nantes	10
10. Saint Pierre, Bruxelles	8
11. W.C.H., Utrecht	7
12. C.H.U., Grenoble	6
13. C.H.U., Nantes	5
14. Centre Pediatrique, Tours	4
Total	238

C.C.M.L. = Centre Chizurgical Marie-Lanne Longue; C.H.U. = Centre Hospitalo-Universitaire; C.H.R. = Centre Hospitalier Regional; W.C.H. = Wilhelmina Children's Hospital.

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number of comparisons, we suggest that tests be interpreted as follows: $p > 0.05$ = not significant (NS); $0.01 < p < 0.05$ = doubtful; $0.001 < p < 0.01$ = significance is likely but needs confirmation by further studies; $p < 0.001$ = highly significant.

Results

Table II indicates the distribution of the pairs of affected members according to degree of the relationship and the kind of defect. The overall concordance rate is 48% for first degree relatives and 28% for second and third degree relatives. Among the 4 monozygous twins, 3 had corcordant lesions.

Statistical analysis concerns the 8 most frequent malformations in first degree relatives (47 concern parent-child pairs and 131 sibspairs). Concordance rates are presented in Table III and the distribution of discordant pairs in Table IV. In each of these tables, we pooled our data with those from other reports: Furhmann[4] and Sanchez-Cascos[5] for concordant pairs (Table III), Furhmann[4] and Fraser and Hunter[2] for discordant pairs (Table IV). The absence of heterogeneity in the distribution of pairs between samples was previously tested.

For each malformation studied, the concordance rates were highly significant, except with VSD, at least in terms of the pooled data (Table III, last column). The distribution of discordant pairs shows some associations to be significantly more frequent than expected (positive associations) and others significantly less frequent than expected (negative associations) (Table IV).

Discussion

Concordant pairs: Our data show that in the majority of congenital heart defects, 2 relatives are more often affected by the same defect than would be expected by chance alone. This finding suggests that congenital heart diseases are not a homogeneous entity, but rather that each kind of defect must be considered

TABLE II Analytical Study of Various Pairs of Association for First Degree Relatives and Those of All Degrees*

	AS	Coarct	PS	PDA	VSD	ASD	AVC	TF	TGA	Trunc	TAPVR	UVH	DORV	Cyan	N Cyan
AS	12	16	1	0	2	9	3	0	2	0	0	0	1	0	3	2
Coarct	1	6	7	2	0	3	2	2	0	0	0	0	0	0	0	1
PS	0	2	8	9	0	0	4	0	6	2	0	0	0	0	2	4
PDA	1	0	0	12	13	4	3	0	2	0	0	0	0	0	1	3
VSD	5	0	0	2	13	18	14	2	13	4	1	0	1	1	3	5
ASD	1	2	4	2	7	13	17	2	6	1	0	2	2	1	4	2
AVC	0	0	0	0	0	2	1	1	0	0	0	0	0	2	1	0
TF	1	0	5	2	12	3	0	14	17	2	3	0	0	1	5	0
TGA	0	0	1	0	3	1	0	2	1	1	0	1	0	1	1	1
Trunc	0	0	0	0	1	0	0	2	0	1	1	0	0	0	2	0
TAPVR	0	0	0	0	0	2	0	0	1	0	0	0	0	0	0	0
UVH	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	
DORV	0	0	0	0	1	0	0	0	1	1	0	0	0	2	0	
Cyan	1	0	2	1	1	1	0	3	1	1	0	0	0	1	0	
N Cyan	1	1	3	3	3	2	0	0	1	0	0	0	0	0	5	

* The diagonal line separates the associations found for first degree relatives (below and to the left of the diagonal) and for all degrees (abo and to the right). Along this line are the concordant pairs. For first degree relatives the number of concordant pairs was 84 and of discordant pai 94. For relatives of all degrees the number of concordant pairs was 106 and of discordant pairs 152.

AS = aortic stenosis; ASD = atrial septal defect; Coarct = coarctation; Cyan = miscellaneous other cyanotic heart diseases; DORV = doub outlet right ventricle; N Cyan = miscellaneous noncyanotic heart disease; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TAPVR total anomalous pulmonary venous return; TF = tetralogy of Fallot; TGA = transposition of the great arteries; Trunc = truncus arteriosus; UV = univentricular heart; VSD = ventricular septal defect.

TABLE III Concordance Rates for First Degree Relatives in 8 Most Common Types of Congenital Heart Disease

Congenital Heart Disease	Present Study			Pooled Data*		
	Pairs (n)†	Concordance (%)	Statistical Test‡	Pairs (n)†	Concordance (%)	Statistical Test‡
VSD	48	27	NS	76	29	NS
ASD	41	32	***	50	36	***
PS	25	32	***	37	35	***
PDA	23	52	***	41	51	***
TF	45	31	***	71	35	***
AS	23	52	***	31	55	***
Coarct	12	50	***	22	32	***
TGA	12	8	NS	28	25	***

* See text for explanation.
† For each heart defect the number of pairs concerns pairs with at least 1 of the 2 numbers affected by this heart disease.
‡ NS = $p > 0.05$ (not significant); *** $p < 0.001$ (highly significant).

as specific and related to a particular mechanism. As for ventricular septal defect (VSD), the low rate of concordance may result from the heterogeneity of this malformation. In this way, genetic data agree with embryologic data which show that VSD may result from abnormalities of different segments of the primitive heart tube: atrioventricular canal, primitive ventricle, or conus.[6]

Positive association among discordant pairs: Tetralogy of Fallot, transposition of the great arteries, and VSD make up a definite "cluster" in our study as in those of others.[2,4,5,6] As these malformations are all consequences of conotruncal abnormalities,[7] some common genes may be considered responsible for the various lesions of the same heart tube segment: the conotruncus. This view fits in with the "segmental approach" recommended by Van Praagh and Van Praagh,[8] and also with the elegant observations of Van Mierop et al[9] in Keeshond dogs. Mating Keeshond dogs with hereditary defects of conotruncal septum, they obtained abnormal embryo hearts with a large spectrum of conotruncal malformations such as VSD, tetralogy of Fallot, truncus arteriosus, and dextroposition of aorta.

In other words, some families appear to possess a conotruncal susceptibility. Defects as different as tetralogy of Fallot, transposition of the great arteries, and VSD may be considered simple subgroups of a basic conotruncal anomaly. It is a first step towards an embryologic concept of congenital heart disease.

Negative associations among discordant pairs: A statistical bias may account for doubtfully significant ($p < 0.05$) negative associations, because relative frequency has been used. However, when significance is high, another explanation should be sought. We suggest that interaction between effects of genes at different loci ("epistasis") is one hypothesis that may account for some of these unexpected observations.

Let us consider in particular the low frequency of pairs of "ventricular septal defect-valvular pulmonary stenosis," which is very surprising in view of the fact that these 2 lesions are so often associated in the same patient within the framework of tetralogy of Fallot. Assuming multifactorial inheritance,[10] we suggest that genes responsible for pulmonary stenosis may favor the expression of genes responsible for VSD and vice versa, the existence of the 2 types of genes in an individual being responsible for tetralogy of Fallot.

TABLE IV Familial Associations Between Discordant Congenital Heart Disease in First Degree Relatives

Association of Congenital Heart Disease	Correlation*	Statistical Test†	
		Present Study	Pooled Data
TF-VSD	+	*	**
TF-PS	+	NS	***
VSD-PS	−	**	***
TF-TGA	+	NS	***
VSD-PDA	−	NS	**
VSD-Coarct	−	NS	***
PS-AS	−	NS	*
PDA-ASD	−	NS	*
PDA-PS	−	NS	**

* + = association more frequent than expected by chance; − = association less frequent than expected by chance.
† NS = $p > 0.05$ (not significant); * $0.01 < p < 0.05$ (doubtful); ** $0.001 < p < 0.01$ (significance is likely but needs confirmation by further studies); *** $p < 0.001$ (highly significant).
Abbreviations as in Table II.

If patient A is affected by isolated pulmonary stenosis, he must have very few VSD genes, otherwise he would have manifested tetralogy of Fallot. Let us consider patient B, who is closely related to A and therefore has a somewhat similar genetic constitution. If he is to be affected, he is likely to have pulmonary stenosis, or if by chance he has more VSD genes than patient A, he would have tetralogy of Fallot but not an isolated VSD.

This hypothesis, which is possibly too schematic and requires confirmation, is compatible with data concerning the observed association between types of malformation in affected relatives: high concordance rates for a given type, positive associations between 2 types having some common genes, negative associations between 2 types due to genes with epistasis effects. However, other models could explain these phenomena as well. In addition, the data are too few to permit a valuable test for any model at the present time.

Conclusion: A statistical analysis of the pairs of congenital heart lesions observed in families with at

least 2 affected members demonstrates nonrandom distribution. In addition to the concordant lesions observed in roughly 50% of cases for first degree relatives, the analysis of discordant lesions shows (1) excess in some pairs, highlighting "clusters" of lesions and suggesting that these lesions, although dissimilar, have some common genetic origin, and (2) deficits in some pairs, which may be a consequence of interaction between effects of genes. This leads us to think of the heart not as a genetic whole but rather as being constituted of different specific genetically determined segments. This concept agrees with the embryologic "segmental approach" suggested by Van Praagh and Van Praagh.[8]

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Left Ventricular Wall Stress in Compensated Aortic Stenosis in Children

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It is known that children with aortic stenosis (AS) frequently have supernormal indexes of left ventricular (LV) pump function and remain compensated for many years. Factors causing this increase in pump performance have not been elucidated. A study was done on LV mechanics in 11 children with AS (aortic valve area 0.5 ± 0.3 cm^2/m^2) and 10 normal subjects. The ejection fraction in the AS group (0.88 ± 0.08) was significantly higher than in normal subjects (0.64 ± 0.08, $p < 0.001$). The mean velocity of fiber shortening was also higher in AS patients (1.80 ± 0.35 circ/s) than in normal subjects (1.22 ± 0.21 circ/s, $p < 0.001$). The end-systolic volume index in patients with AS (9 ± 8 ml/m^2) was much lower than in normal subjects (27 ± 8 ml/m^2). LV mass in patients with AS was 180 ± 58 g/m^2 compared with 96 ± 9 in normal subjects. LV wall stress was reduced throughout the cardiac cycle in patients with AS. Peak stress in patients with AS was 238 ± 51 dynes/$cm^2 \cdot 10^3$ versus 439 ± 85 in normal subjects. The end-systolic stress–end-systolic volume index ratio, an indicator of contractile state, was not elevated in patients with AS. It is suggested that diminished wall stress in concert with normal contractile function permits the supernormal pump function seen at rest in children with AS.

The performance of the pressure-overloaded heart, a subject of recent controversy, has been described by the intrinsic function of the contractile mechanism and by its pump function as assessed by ejection indexes. It is clear that hypertrophy and other compensations maintain pump function in the initial stages of pressure overload, but if overload is excessive and prolonged, pump function eventually fails. Recent animal[1–16] and human[17–27] studies show that contractile muscle function varies from normal in some pressure-overloaded hearts to depressed in others. Some studies in animals have even shown supernormal pump function[10] and have suggested increased contractile muscle function[23] in experimental pressure overload. It is recognized that children with aortic stenosis (AS) have supernormal pump function and remain compensated for many years.[28–30] We wanted to know what specific changes in ventricular mechanics or cardiac muscle characteristics permit this supernormal pump performance and how this information is related to what is known about ventricular mechanics and muscle function in other forms of pressure overload. Therefore, we assessed left ventricular (LV) ejection indexes, loading conditions, wall stress, and contractile muscle function in children with AS.

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Methods

Patient groups: Two patient groups were established: 11 patients with AS (mean age 10 ± 3.6 years, mean body surface area 1.12 ± 0.33 m^2) and 10 normal patients (mean age 8.5 ± 2.9 years, mean body surface area 1.15 ± 0.24 m^2). All were studied by cardiac catheterization.

Eight patients with AS had valvular obstruction; 1 had a subvalvular membrane and 2 had supravalvular obstruction. All were asymptomatic with no previous history of chest pain, heart failure, syncope, associated cardiac lesions, or cardiac surgery. Aortic regurgitation was excluded by aortic root angiography.

The normal patients were all asymptomatic and underwent cardiac catheterization to exclude significant heart disease suggested by physical examination and noninvasive testing. All proved free of cardiac disease.

Catheterization and ventricular performance analysis: Catheterization was performed from the femoral vessels under light sedation with a mixture of meperidine, promethazine, and chlorpromazine. The aortic valve was crossed by the retrograde approach; because the smaller femoral artery diameter in children may be associated with vascular compli-

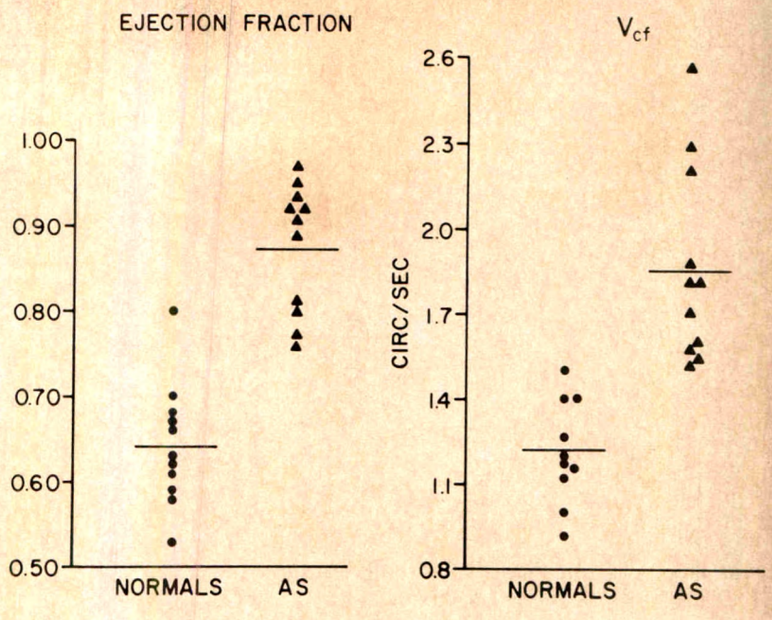

FIGURE 1. Ejection fraction and Vcf for normal subjects (**circles**) and patients with AS (**triangles**) shown. Both are significantly increased in aortic stenosis. The **horizontal line** represents the mean value for each patient group.

cations, a second arterial catheter to provide simultaneous LV and aortic pressures was not employed. Pressure tracings were obtained from the left ventricle and ascending aorta by a fluid-filled catheter system and recorded at 75 or 100 mm/s with a simultaneous electrocardiogram. The LV pressure was obtained just before angiography. To determine the time difference between a micromanometer-tipped system and fluid-filled catheters, we measured pressures simultaneously with both catheters in 17 randomly chosen cardiac cycles in 2 dogs. The time delay in peak LV pressure from micromanometer to fluid-filled catheters was 13.2 ± 3.1 ms, a delay of <1 cineangiographic frame. Because this does not significantly alter the relation of pressure to volume, especially at end systole, no time-lag correction was used.[17,31] The transvalvular gradient was obtained by planimetering superimposed aortic and LV pressure traces recorded sequentially before angiography. A mean cardiac output was calculated from Fick determinations obtained early in the course of the catheterization; heart rate during Fick determinations and pressure-volume analysis agreed within 11 beats/min in all cases and 7 beats/min in most cases. The aortic valve area was estimated from the Gorlin formula and indexed by body surface area.[32]

Single-plane LV angiograms were performed in the anteroposterior projection (9 patients) and right anterior oblique projection (2 patients) filmed at 60 frames/s. LV volumes were calculated utilizing a digitizer, the area-length method, and regression equations for the respective projections.[33,34] Volumes were indexed by body surface area. End-diastolic volume was defined as the largest volume measured in a cardiac cycle. End-systolic volume was measured at the time of aortic valve closure, which corresponded to the smallest volume in every case. Wall thickness was measured at end-diastole at midcavity level. Because we recognized the practical and theoretical difficulties of measuring small end-systolic volumes accurately, we determined intra- and interobserver variation and compared our angiographic end-systolic volumes with those calculated from the end-diastolic volume, Fick cardiac output, and heart rate. Maximal intraobserver variation was 5 ml at end-diastole and 2 ml at end-systole. Maximal interobserver variation was 7 ml at end-diastole and 5 ml at end-systole. The mean end-systolic volumes calculated by angiographic and Fick methods were nearly identical ($Y = 1.1 X + 0.2$, $r = 0.93$). Ejection fraction was calculated in the usual manner. The mean velocity of circumferential fiber shortening (Vcf) was obtained using the formula $Vcf = (EDD - ESD)/(EDD \cdot ET)$, where EDD is the end-diastolic minor axis, ESD is the end-systolic minor axis, and ET is the ejection time measured from the upstroke of the aortic pressure trace to the dicrotic notch. LV mass was calculated by the method of

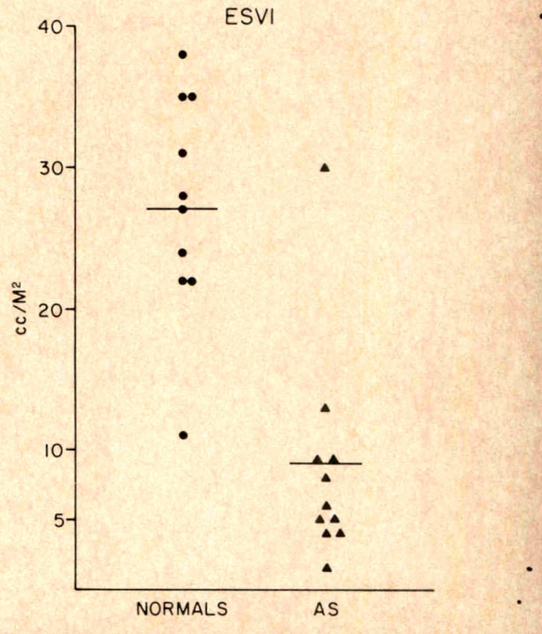

FIGURE 2. End-systolic volume index is much lower in patients with AS (**triangles**) than in normal subjects (**circles**). The **horizontal line** represents the mean value for each patient group. ESVI = end-systolic volume index.

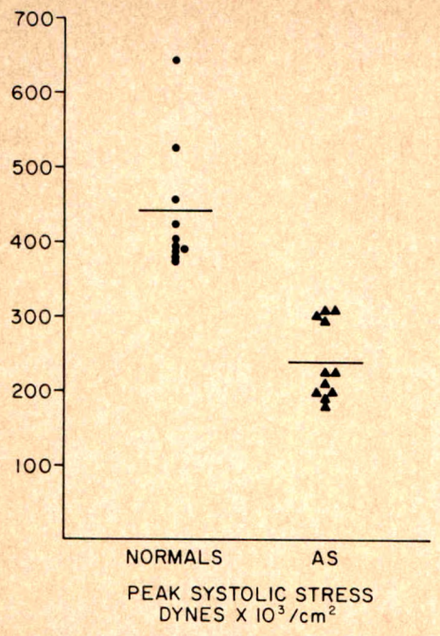

FIGURE 3. Peak wall stress in patients with AS (**triangles**) is significantly lower than that in normal subjects (**circles**). The **horizontal line** represents the mean value for each patient group.

Kennedy et al.[33] Stroke work index was calculated using the formula stroke work index = mean LV pressure × stroke volume index × 0.0136 g·m/mm Hg, where mean LV pressure is obtained from the sum of the mean aortic pressure and transvalvular gradient and the stroke volume index was obtained angiographically.

The cycle length of aortic and LV pressure traces and angiographic beats were then examined, and beats with a common cycle length were selected. Extra- and postextrasystolic beats were excluded. In no instance did pressure or angiographic cycle lengths differ by more than 10 ms. A frame-by-frame analysis of ventricular wall stress was performed for the entire cardiac cycle using the Hugenholtz[35] approximation for wall thickness during systole, the formula of Mirsky[36] and the computer-assisted method of Gunther and Grossman.[27] End-systolic stress was taken at end-systole as previously defined and peak stress was defined as the maximal stress present in the cardiac cycle. Mean systolic stress was calculated by obtaining the area under the stress-time curve between end-diastole and end-systole and dividing by this time interval. The use of mean systolic stress further minimizes the error introduced into the time course of stress development as measured by fluid-filled catheters.[27]

To validate our methods further, we studied 2 patients with AS utilizing a micromanometer-tipped catheter in the left ventricle and simultaneous pressure-volume data obtained by examining the levophase of a main pulmonary artery angiogram.[28]

Data from normal subjects were analyzed in an identical fashion.

Statistical analysis: All values were expressed as mean ± 1 standard deviation. Measured and calculated results for the AS and normal groups were evaluated using an unpaired t test. Linear regression was performed by the method of least squares.

Results

Hemodynamic data: The mean LV to aortic peak gradient was 109 ± 43 mm Hg and the mean calculated aortic valve area was 0.5 ± 0.3 cm^2/m^2. There was no significant difference between the heart rates in the AS (103 ± 23 beats/min) and normal groups (100 ± 26 beats/min).

Pump function: The cardiac index was similar in the 2 patient groups (4.7 ± 1.8 liters/min/m^2 in the patients with AS, 5.2 ± 1.6 in the normal subjects). Figure 1 shows that the ejection fraction and mean Vcf were significantly higher in the AS patients (0.88 ± 0.08, 1.80 ± 0.35 circ/s) than in the normal subjects (0.64 ± 0.08, 1.22 ± 0.21, $p < 0.001$). The stroke work index was also

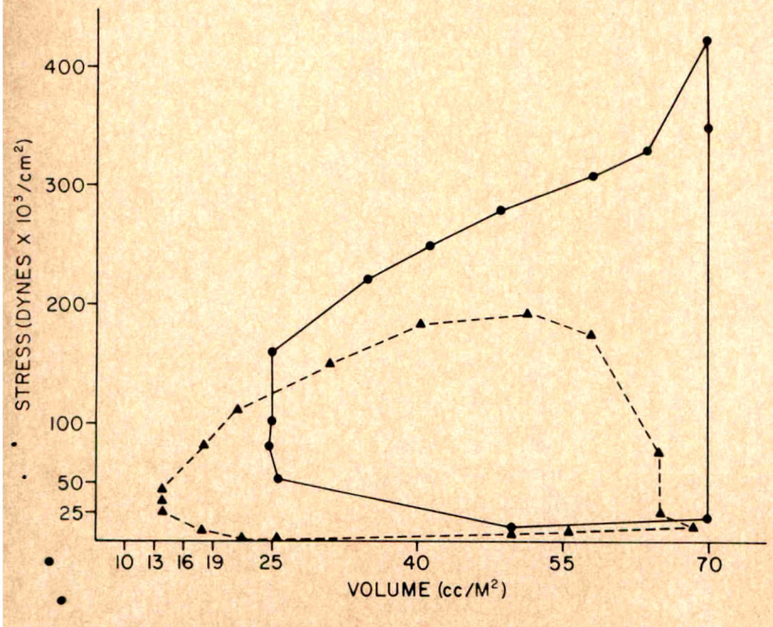

FIGURE 4. Frame-by-frame values for wall stress are plotted against the left ventricular volume index for a normal subject (**circles**) and a patient with AS (**triangles**) who had similar end-diastolic volumes. Note that throughout the cardiac cycle, wall stress was lower in the patient with AS. End-systolic volume was also reduced in the patient with AS.

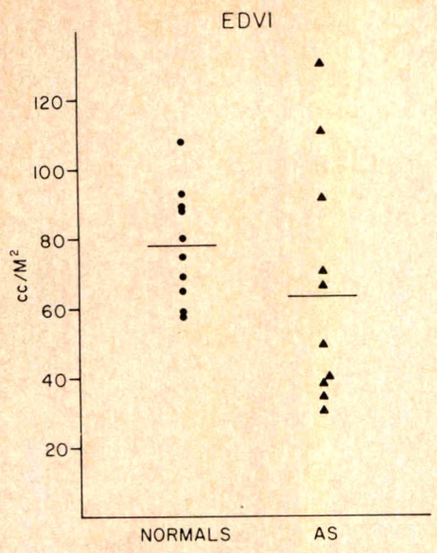

FIGURE 5. End-diastolic volume index (EDVI) for patients with AS (**triangles**) and normal subjects (**circles**). A wide overlap is demonstrated. The **horizontal line** represents the mean value for each patient group.

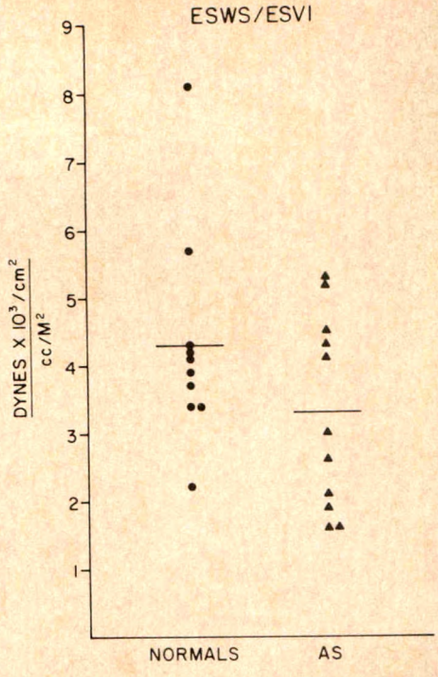

FIGURE 6. The end-systolic wall stress–end-systolic volume index ratio for patients with AS (**triangles**) and normal subjects (**circles**). There is no significant difference. The **horizontal line** represents the mean value for each patient group. ESVI = end-systolic volume index; ESWS = end-systolic wall stress.

higher in the AS patients (91 ± 49 g·m/m^2) than in the normal subjects (50 ± 12 g·m/m^2, p = 0.02).

Ventricular mechanics: In an effort to explain the increased pump performance, we examined LV pressure, wall thickness, muscle mass, volume, wall stress, and contractile indexes.

LV peak systolic pressure in the AS group (193 ± 46 mm Hg) was significantly higher than the value in normal subjects (105 ± 11 mm Hg, p <0.001). End-diastolic pressure was within the normal range in all patients.

There was extensive hypertrophy in the AS group. LV mass index was significantly increased in the AS group (180 ± 58 g/m^2) compared with normal subjects (96 ± 9, p <0.001). Wall thickness was similarly doubled in the AS group (1.13 ± 0.26 cm) compared with that in the normal patients (0.51 ± 0.1, p <0.001).

The end-systolic volume index was much lower in the AS group (9 ± 8 ml/m^2), averaging one third of the normal value (27 ± 8, p <0.001) (Fig. 2).

Peak systolic stress was strikingly reduced in the AS group (238 ± 51 dynes/cm^2·10^3), averaging approximately half the normal value (439 ± 85, p <0.001) (Fig. 3). End-systolic stress in the AS group (24 ± 12 dynes/cm^2·10^3) was less than one fourth the normal value (109 ± 30, p <0.001). Mean systolic stress was also lower in the AS group (126 ± 26 dynes/cm^2·10^3) than the normal group (327 ± 58, p <0.001). Systolic stress was reduced at all points throughout systole as demonstrated in the stress-volume loops of Figure 4.

The end-diastolic volume index was slightly lower in the AS group but varied widely from patient to patient and overlapped in the 2 groups (Fig. 5).

The ratio of LV wall stress to LV volume index at end-systole was used as an estimate of LV contractile muscle function. There was substantial overlap in the individual values for the ratio of end-systolic wall stress to end-systolic volume index in the 2 groups of patients, as shown in Figure 6. None of the values for this ratio in the AS patients were higher than the highest value in the normal group.

Results obtained in 2 patients with AS utilizing micromanometer-tipped catheters and simultaneous pressure-volume data were consistent with the findings in the AS group. The respective LV to aortic gradients were 99 and 81 mm Hg, end-diastolic volume indexes 49 and 68 ml/m^2, end-systolic volume indexes 5 and 13 ml/m^2, ejection fractions 0.90 and 0.81%, and Vcfs 1.65 and 1.57 circ/s. Peak systolic stresses were 229 and 212 dynes/cm^2·10^3, end-systolic stresses were 48 and 36 dynes/cm^2·10^3, and the ratios of end-systolic stress to end-systolic volume index were 9.6 and 2.8, respectively.

Discussion

An important finding of this study is that LV wall stress in children with AS is lower than normal throughout systole. This occurs despite much higher systolic pressures in AS patients. Previous studies in adults with compensated pressure overload have shown that wall thickness increases, offsets the pressure overload, and maintains normal wall stress.[37,38] However, in our children with AS, increases in wall thickness appear to have provided overcompensation for the pressure overload.

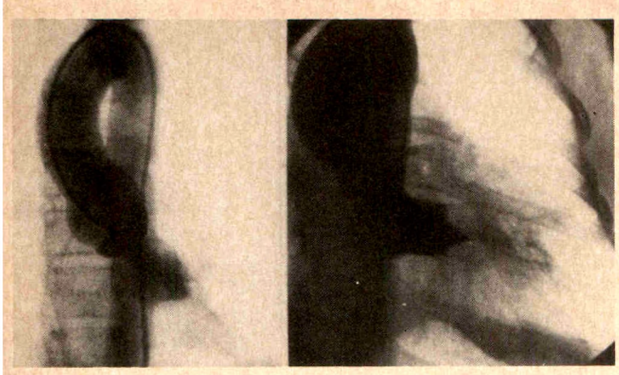

FIGURE 7. End-systolic frames from 2 patients with aortic stenosis. The end-systolic volume index in the left frame is 9 ml/m^2 and in the right frame, 3 ml/m^2.

We also found ejection fraction and Vcf were increased in these children, corroborating previous reports.[28–30] The observed subnormal wall stress, acting to reduce LV afterload, may have permitted the supernormal pump performance. This is probable since it is well known that a reduction in afterload will increase ejection fraction and Vcf while decreasing end-systolic volume.[27,39–42] Our patients with AS had a striking reduction in end-systolic volume (Fig. 7). In 9 of 11 patients, end-systolic volume index was <10 ml/m^2. While calculation of such small volumes is prone to error, the variation of end-systolic volume index needed to significantly reduce ejection fraction and increase end-systolic stress is far beyond our inter- and intraobserver error. Our very small end-systolic volumes are also corroborated by the Fick method as well as direct inspection of the end-systolic frames in Figure 7.

It is unlikely that the large increase in pump performance was provided by increased preload, since the end-diastolic volume was normal or low in the AS patients. This increased pump performance could also have resulted from a similarly large increase of contractile muscle function. This did not appear to occur since the end-systolic stress-volume ratio in AS patients overlapped extensively with that in normal subjects. The relation between afterload and volume at end-systole has been proposed as a contractile index which is thought to be relatively independent of loading conditions.[40,43–49] As shown in Figure 6, we used the ratio of end-systolic wall stress to end-systolic volume index as an estimate of contractile muscle function. We recognize the limitation of estimating contractile muscle function by this method. Although this ratio is probably less accurate than manipulating patients through a range of loading conditions to obtain the slope of the end-systolic stress-volume relation, we have found this ratio clinically useful and a valid approximation of the *true* end-systolic relation.[26,50–52] This should allow us to exclude the large increases in contractile muscle function that would be required to explain our patients' increased pump performance due to increased contractile muscle function alone.

How do the current data fit in with and add to what is known about pump and contractile muscle function in other examples of pressure-overloaded hearts? Taken together, the data of previous animal and human studies suggest a pathologic continuum from the one extreme of poorly functioning muscle in a pressure overloaded heart with impaired pump function to the other extreme of normally functioning muscle in a pressure overloaded heart with normal or even excessive pump function. At one extreme, when ventricular pressure overload is chronic and severe, heart failure occurs and contractile function is depressed.[2,4,7,8,12,13,17–21] In the middle ground, contractile and pump function may be normal or abnormal. There may be normal contractile function in an excessively overloaded heart where hypertrophy does not normalize ventricular wall stress and pump function is thereby reduced.[18,19,27] In animal and human experiments there may be moderately depressed contractile function in an adequately hypertrophied pressure-overloaded heart which has normal pump function at rest.[2,5,7,8,17,18] At the other extreme, in experimental animals when pressure overload is less severe, pump function is normal or supernormal and contractile function is usually normal.[1,3,9–11] Our data appear to fit in with the above observations at the positive extreme of the proposed pathologic continuum by showing supernormal pump function and normal contractile function, findings not previously reported in man. Unlike experimental animals, however, pressure overload in our AS patients was severe.

The significance of our findings is unclear. It may well be that although stress is subnormal at rest, it becomes normal when higher LV pressures develop during exercise and the LV has adapted to these higher loads. One can speculate that this "stress reserve" is a factor which helps maintain the prolonged period of hemodynamic compensation seen in children with AS.

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Measurement of Systemic and Pulmonary Blood Flow And QP/QS Ratio Using Doppler and Two-Dimensional Echocardiography

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A noninvasive method for measuring systemic and pulmonary blood flow using Doppler velocimetry combined with 2-dimensional (2-D) echocardiography has been developed. High correlations were found between Fick- and Doppler-derived indexed measurements of systemic and pulmonary flow as well as the pulmonary to systemic flow ratio in 33 patients undergoing cardiac catheterization (systemic flow [n = 28], r = 0.78; pulmonary flow [n = 21], r = 0.88; Qp/Qs ratio [n = 24], r = 0.85). The random errors of the 2 methods were not significantly different. Outflow tract obstruction, semilunar valve regurgitation, and patent ductus arteriosus were the only lesions in which limitations to the use of this method were encountered. We anticipate that this method will be of use in initial and serial evaluations of adult and pediatric patients with low cardiac output or intracardiac shunts.

Pulsed Doppler velocimetry, used in conjunction with 2-D echocardiography, has received increasing attention as a tool for noninvasive measurement of blood flow. Steingart et al[1] demonstrated that the area under the aortic Doppler frequency-time curve is proportional to left ventricular stroke volume in dogs. Hoenecke et al[2] reported estimation of cardiac output using pulsed Doppler for measurement of flow velocity and angiography for measurement of vessel diameter. Bommer et al[3] and Magnin et al[4] reported estimation of cardiac output in adults using pulsed Doppler and 2-D echocardiography.

We have developed a method for measuring blood flow in both the aorta and pulmonary artery, using a relatively low transmitted frequency which enables detection of high flow velocity and increases the operating depth of the range-gated system. Furthermore, Doppler velocity measurements were facilitated by selecting transducer positions that allow the ultrasonic beam to be aligned parallel to the direction of blood flow, eliminating the need to measure the incident angle. This report describes our method for measuring systemic and pulmonary blood flow and pulmonary to systemic flow ratio (Qp/Qs) and compares its performance with simultaneous determinations of blood flow using the Fick principle.

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Methods

Subjects: Thirty-three patients aged 2 weeks to 23 years (median 9 months) and weighing 2 to 83 kg (median 7) underwent measurement of systemic or pulmonary blood flow, or both, using Doppler at the time of cardiac catheterization between November 1981 and March 1982. The cardiac lesions included ventricular septal defect (13 patients), complete common atrioventricular canal (8 patients), valvular pulmonary stenosis (3 patients), valvular aortic stenosis (2 patients), atrial septal defect (2 patients), tetralogy of Fallot (1 patient), tetralogy of Fallot after repair (1 patient), anomalous origin of the left coronary artery from the pulmonary artery (1 patient), transposition of the great arteries after Senning repair (1 patient), and hepatic arteriovenous malformation (1 patient). Patient selection was based on (1) absence of significant patent ductus arteriosus, (2) stability of the patient during measurements, and (3) absence of complex anatomic or physiologic features that would make the usual Fick calculations inapplicable, such as uncorrected transposition of the great arteries.

Procedure: Each patient initially underwent echocardiographic examination using a Picker Echoview 80 CI with a mechanical sector scanner and a 5.0 or 3.5 MHz transducer (active element diameter 13 or 19 mm; focal length 5 or 9 cm)[5,6] for measurement of the diameter of the proximal ascending aorta and main pulmonary artery. Subxiphoid views

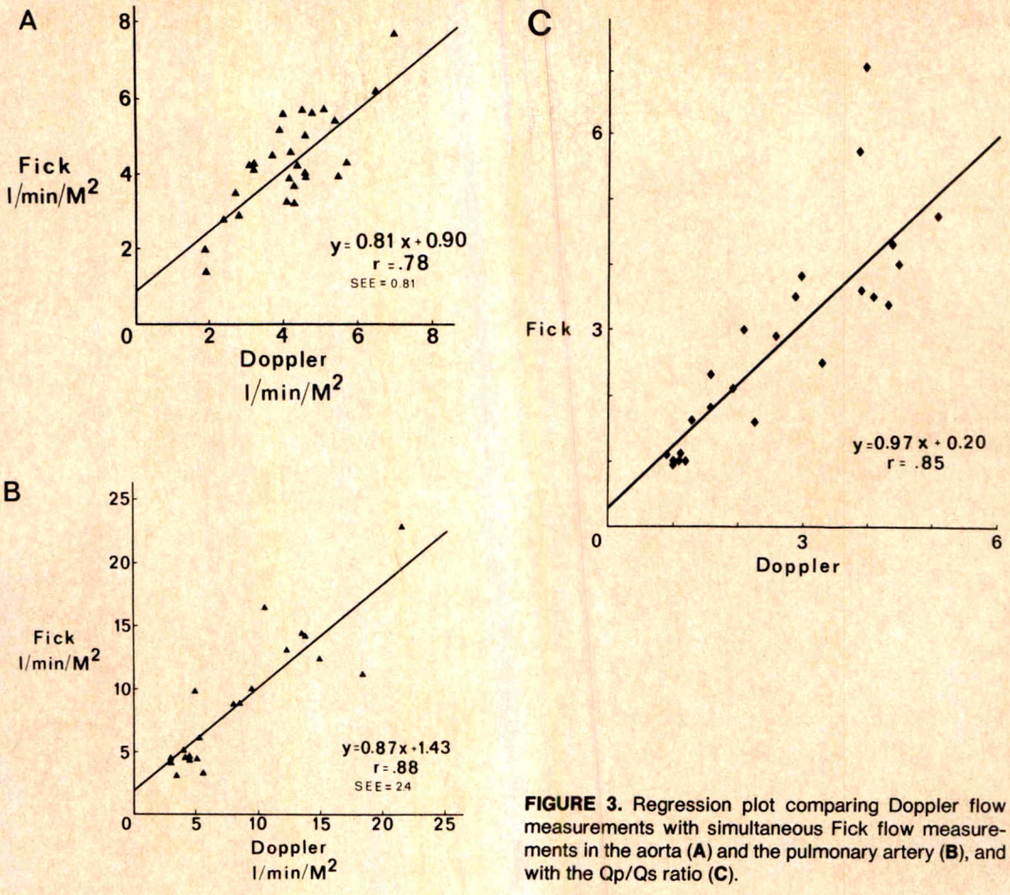

FIGURE 3. Regression plot comparing Doppler flow measurements with simultaneous Fick flow measurements in the aorta (**A**) and the pulmonary artery (**B**), and with the Qp/Qs ratio (**C**).

the random error of the Doppler method is not significantly different from the random error of the Fick method. Moreover, Doppler and 2-D echocardiography are noninvasive and easily repeatable.

Outflow tract stenosis, semilunar valve regurgitation, and patent ductus arteriosus are the only limitations to the use of this method encountered thus far. Turbulence and extremely high velocity flow due to stenotic lesions cause signal aliasing and spectral broadening. Semilunar valve regurgitation results in an overestimation of flow due to failure to measure the regurgitant volume. Our previous observations indicate that with patent ductus arteriosus, the systemic flow is overestimated and pulmonary flow underestimated because of the location of the aortopulmonary connection distal to the points of sampling in the pulmonary artery and the aorta. There was no difficulty in identifying patients with outflow tract stenosis, in whom the Doppler method was not applicable, because even relatively mild stenosis produces marked distortion of the frequency-time plot. Significant semilunar regurgitation was evident when retrograde diastolic flow was detected in the subvalvular area. However, patent ductus arteriosus may be difficult to identify in the presence of other defects and may lead to underestimation of pulmonary flow and Qp/Qs ratio.

Although previous investigators[2–4] have not done so, we have reported our results based on flow measurements indexed for body surface area. We believe that indexed volumes should be used for comparative studies because (1) indexed outputs are more meaningful and more commonly encountered clinically, and (2) comparison of unindexed outputs allows the variation in the size of the patients to "improve" the apparent correlation between invasive and noninvasive measurements.

Although measurement of blood flow in the aorta and pulmonary artery using Doppler techniques seems straightforward in principle, attempts to develop useful clinical methods have encountered numerous practical problems. These include (1) measurement of the great artery dimensions and adjustment for systolic expansion, (2) compensation for the angle between the ultrasonic beam and the direction of blood flow, (3) adjustment for differences between the peak velocity of flow measured by Doppler shift and the actual average velocity of flow as determined by the velocity profile within the vessel, (4) the conflicting requirements for pulse repetition frequency imposed by the need to measure high flow velocities at a large sampling depth, and (5) the limited availability of reliable real-time signal processing.

Vessel dimensions: We used high resolution 2-D echocardiography to obtain the maximal systolic great artery diameter and used that value to calculate the cross-sectional area of the vessel. Previous studies have shown that the cross-sectional area of the aorta increases 5 to 10% during systole, while that of the pul-

onary artery increases 2 to 18%.[10–12] The increase in ameter occurs early in systole, concomitant with the ostroke of the pressure tracing, so that most antero-ade flow in the ascending aorta or pulmonary artery curs when the vessel is at or near its peak systolic di-ension.[11]

Incident angle: We aligned the Doppler beam par-lel (within 20°) to the direction of blood flow. The oppler shift is proportional to the cosine function of e incident angle, which approximates unity for angles ss than 20° (>0.94). Under these conditions, the in-antaneous peak frequency of the Doppler signal anslates directly to the instantaneous peak velocity blood flow, as described by the Doppler equation.[1]

Velocity profile: In order to calculate blood flow, the elocity profile in the artery must be such that the peak elocity of blood flow, as represented by the envelope the Doppler frequency-time curve, is proportional to ıe mean velocity of flow and the proportionality con-ant must remain the same throughout systole. Pre-ous studies have shown that the flow profile in the scending aorta is quite flat for several centimeters ove the valve.[13] Therefore, we confined our sampling te to the immediate supravalvular area and assumed ıat the peak and mean velocities were equal through-ıt systole. This practice undoubtedly results in a slight erestimation of mean flow velocity. Again we assumed ıat conditions in the pulmonary artery were the same those in the aorta.

Pulse repetition frequency: The sampling theorem ates that for the returning Doppler-shifted signals to e faithfully reconstructed, the pulse repetition fre-ıency must be at least twice the highest frequency ıift encountered.[14] The Doppler frequency shift is rectly proportional to the velocity of blood flow, so ıat for any transmitted frequency, the minimal pulse petition frequency must increase as the velocity of ow increases. However, the maximal sampling depth inversely proportional to the pulse repetition fre-ıency because of the finite transit time of the pulsed gnal. Because the Doppler frequency shift is also di-ctly proportional to the transmitted frequency, the se of a lower transmitted frequency decreases the oppler shift produced by any given velocity of blood ow and concomitantly decreases the minimal pulse repetition frequency required for faithful reproduction of the signal. We found that a 1.5 MHz transducer is an acceptable compromise which provides adequate sampling depth on the one hand and unambiguous velocity measurements on the other.

Signal processing: The introduction of fast Fourier, transform-based spectrum analyzers has provided essentially real-time analysis and display of the Doppler quadrature output. These devices avoid the inherent inaccuracies of zero-crossing detectors, the bulk and expense of banked filters, and the inconvenience of off-line analysis. The output display of the analyzer used in this study is a frequency-time plot with amplitude displayed as shades of gray. We have found that in the absence of outflow tract obstruction, there is a well defined maximal frequency envelope that can easily and reproducibly be traced.

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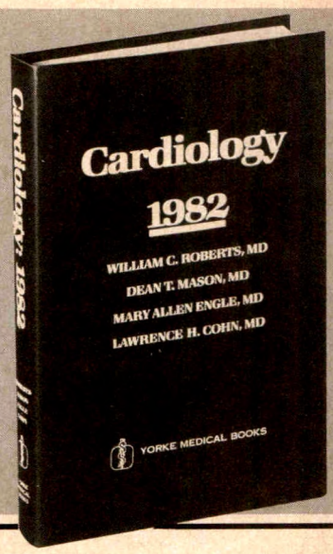

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CONTRAINDICATIONS

onchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and er than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary lmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is sec- ry to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic- henting psychotropic drugs (including MAO inhibitors), and during the two week lrawal period from such drugs.

WARNINGS

DIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the ntial hazard of further depressing myocardial contractility and precipitating cardiac e. In patients already receiving digitalis, propranolol may reduce the positive inotropic n of digitalis and may have an additive depressant effect on AV conduction.

PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac e has developed during propranolol therapy. At the first sign of impending cardiac e, patients should be fully digitalized and/or given a diuretic, and observed closely. ardiac failure continues, despite adequate digitalization and diuretic therapy, pro- olol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, nts should be maintained on combined therapy and closely followed until threat of ac failure is over.

PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of gina and, in some cases, myocardial infarction, following *abrupt* discontinuation of DERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage ould be gradually reduced and the patient carefully monitored. In addition, when DERAL is prescribed for angina pectoris, the patient should be cautioned against rruption or cessation of therapy without the physician's advice. If INDERAL therapy nterrupted and exacerbation of angina occurs, it usually is advisable to reinstitute DERAL therapy and take other measures appropriate for the management of unsta- angina pectoris. Since coronary artery disease may be unrecognized, it may be ident to follow the above advice in patients considered at risk of having occult ath- sclerotic heart disease, who are given propranolol for other indications.

PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use not been adequately appraised. Give special consideration to propranolol's potential ggravating congestive heart failure. Propranolol may mask the clinical signs of devel- or continuing hyperthyroidism or complications and give a false impression of ovement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be fol- d by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Pro- olol does not distort thyroid function tests.

PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been ted in which, after propranolol, the tachycardia was replaced by a severe brady- a requiring a demand pacemaker. In one case this resulted after an initial dose of propranolol.

PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be rawn 48 hours prior to surgery. In case of emergency surgery, the effects of pro- olol can be reversed by administration of beta-receptor agonists such as isopro- ol or levarterenol, but such patients may be subject to protracted severe hypotension. ulty in restarting and maintaining the heart beat has been reported.

PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRON- IS, EMPHYSEMA), administer with caution, since propranolol may block bronchodila- roduced by endogenous and exogenous catecholamine stimulation of receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

—Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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8028/882

Long-Term Failure Rate and Morphologic Correlations In Porcine Bioprosthetic Heart Valves

FREDERICK J. SCHOEN, MD, PhD, JOHN J. COLLINS, Jr., MD, and LAWRENCE H. COHN, MD

To ascertain relations among site, incidence, and mechanisms of clinically evident failure of porcine bioprosthetic heart valves, the frequency of failure of 1,110 valves in 1,001 adult operative survivors from January 1972 to January 1982 was reviewed and correlated with the pathologic features of 22 consecutive dysfunctional valves. There were 373 mitral, 519 aortic, and 109 double replacements, yielding for study 482 mitral and 628 aortic valves at risk. Infective endocarditis occurred in 1.9% (8 mitral, 7 aortic, and 4 double). Twenty-three valves (13 mitral and 10 aortic) with documented primary dysfunction were explanted, a mean of 55 months (range 9 to 94) after surgery. The primary dysfunction rate for the 333 valves implanted for ≥5 years was 6.8% (11 of 161) for mitral and 4.1% (7 of 172) for aortic valves. Valves implanted for <5 years had a failure rate of 0.7%. The actuarially determined freedom from primary valve failure wa 98 ± 1% for mitral and 98 ± 1% for aortic valve at 5 years and 79 ± 7% for mitral and 91 ± 4% fo aortic valves at 10 years. Recovered valves (1 mitral and 10 aortic) with detailed morphologi analysis were functioning for a mean duration of 5 months (range 12 to 87). Causes of failure include calcification-related tears in 7 (4 mitral and 3 aortic mean 66 months), tear without calcium deposits i 4 (4 mitral, mean 44 months), cuspal stiffenin without tear but with calcium deposits in 2 (1 mitra and 1 aortic, mean 80 months) and thrombosis in (aortic). Late primary dysfunction was most fre quently a result of degenerative processes, espe cially calcification, often with secondary tears, bu cuspal tears in the absence of calcium deposits an thrombosis predominated at shorter intervals.

Since their introduction in 1970, glutaraldehyde-preserved porcine aortic valve bioprostheses have performed satisfactorily in most adult patients for up to 10 years.[1–5] Nevertheless, they often fail relatively early in children,[6–10] and there is considerable uncertainty regarding the frequency of late dysfunction in adults. Although morphologic aspects of valve degeneration and dysfunction have been described,[11–15] the mechanisms of such failure remain poorly understood. This report examines the failure rate of 1,110 glutaraldehyde-preserved porcine bioprostheses in 1,001 operative survivors at the Brigham and Women's Hospital (formerly the Peter Bent Brigham Hospital) between January 1972 and January 1982, and correlates these data with the pathologic features of 22 consecutivel analyzed failed valves, to obtain relations among site incidence, and mechanisms of failure.

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Methods

Clinical: The clinical characteristics of the 1,074 adul patients who underwent intracardiac valve replacement witl the Hancock porcine bioprosthetic heart valve during th study period are summarized in Table I. The 1,001 operativ survivors (93% overall survival rate)—373 with mitral, 51 with aortic, and 109 with double valve replacements—forn the basis of the clinical portion of this study. For portions o this analysis, the mitral and aortic valves implanted in pa tients undergoing simultaneous aortic and mitral valve re placement are added to the numbers of single valves at eacl location. Thus, there were 482 mitral plus 628 aortic (total o 1,110) valves at risk for failure. During this period porcin bioprosthetic valves were used to replace cardiac valves in 66% of all adults operated on for valvular heart disease at ou hospital.

All patients undergoing bioprosthetic mitral valve re placement, either alone or in combination with aortic valv replacement, were given the anticoagulant warfarin sodiun for 4 to 6 weeks postoperatively. Warfarin was then graduall

ABLE I Clinical Data

	MV	AV	MV + AV	Total
ıtients	408	547	119	1,074
ıle/female	146/262	401/146	60/59	607/467
ge (yr)				
Mean	57	60	57	57
Range	20–86	16–87	19–79	16–87
sociated procedures: total/CABG	117/85	182/136	18/11	317/232
erative mortality	35 (9%)	28 (5%)	10 (8%)	73 (7%)
erative survivors	373	519	109	1,001

AV = aortic valve; CABG = coronary artery bypass grafting; MV = mitral valve.

ABLE II Primary Valve Dysfunction: Frequency and Clinical Variables

	Mitral	Aortic	Total
Valves at risk	482	628	1,110
Valves with primary dysfunction	13 (2.7%)	10 (1.6%)	23 (2.1%)
Time to reoperation (mo)			
Mean	68	38	55
Range	9–94	18–82	9–94
Age at implantation (yr)			
Mean	48	50	49
Range	35–68	18–82	18–82

pered over a 2-week period unless the patient had an in-
acardiac thrombus or an enlarged left atrium with chronic
rial fibrillation. No patient with an aortic bioprosthesis was
ven anticoagulant medication initially after surgery.

Follow-up data were obtained by patient examination or
report from the family physician or cardiologist and were
mpleted between December 1981 and March 1982. Causes
death were determined from hospital autopsy records,
roner reports, or, where necessary, clinical data only. Valve
llure was defined as clinically evident dysfunction due to
imary tissue failure with or without calcification, critical
enosis with or without stent creep, thrombosis, or infective
docarditis. The details of the statistical analysis, in which
e cumulative probability of valve dysfunction was estimated
ing the life-table model, were previously reported.[4] All
merical data are reported as the mean ± standard error of
e mean.

Pathology: The failure modes of 22 consecutive dysfunc-
nal Hancock porcine bioprostheses obtained at reoperation
various indications (19) or at autopsy (3) of 21 patients
ring a 2-year period at our hospital were analyzed. There
re 12 mitral and 10 aortic valves implanted for a mean of
months (range 12 to 87) in patients with a mean age of 50
ars (range 22 to 68). During this period 3 additional
oprostheses (all mitral) were surgically explanted for
ravalvular leaks; they are not included in this study. Some
ostheses removed at our hospital and analyzed in the mor-
ologic portion of this study were originally implanted at
her hospitals.

Each valve received was fixed in formalin, described grossly,
otographed from both inflow and outflow aspects, and ra-
ographed (40 kV by 0.8 min) (Faxitron Model 43805, Hew-
t-Packard, McMinnville, Oregon). Multiple specimens were
ken of the valve cusps at their centers and at their com-
issures, embedded in either paraffin or glycolmethacrylate
edium (JB4, Polysciences, Warrington, Pennsylvania) or
th, sectioned at 6 μm (paraffin) or 1 to 3 μm (plastic), and
ained with hematoxylin and eosin. Selected sections were
ained with Gram's stain (for bacteria) or by von Kossa's method (for calcium phosphate). Additional decalcified specimens were embedded in paraffin, sectioned, and stained.

Results

Frequency of dysfunction: The frequency of primary valve dysfunction for both mitral and aortic bioprostheses and the clinical characteristics of the patients in whom these valves were dysfunctional are summarized in Table II. In the total group of 482 mitral and 628 aortic valves, the frequency of primary valve dysfunction was 2.7% for mitral and 1.6% for aortic, an overall frequency of 2.1%.

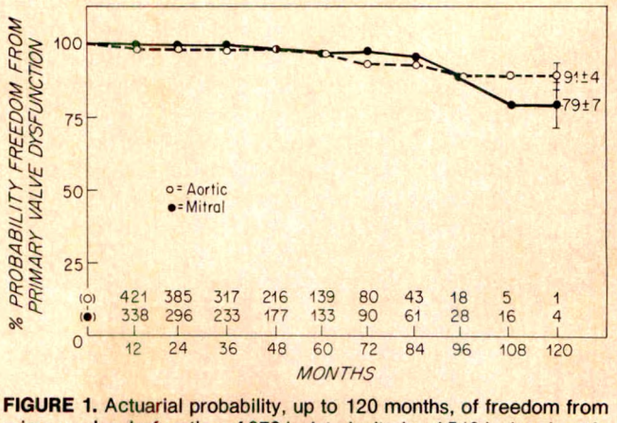


FIGURE 1. Actuarial probability, up to 120 months, of freedom from primary valve dysfunction of 373 isolated mitral and 519 isolated aortic valve replacements including all intrinsic valve failures in the absence of infective endocarditis. **Figures above the time axis** denote numbers of patients at risk at each time interval. **Bars** denote value ± standard error of the mean.

TABLE III Temporal Incidence of Primary Valve Dysfunction (PVD)

Year of Surgery	Mitral Bioprostheses: At Risk/With PVD	Aortic Bioprostheses: At Risk/With PVD	All Prostheses: At Risk/With PVD
1972	17/2	15/0	32/2
1973	28/4	18/0	46/4
1974	34/2	30/3	64/5
1975	41/3*	47/1*	88/4*
1976	41/0	62/3	103/3
Total implanted 5–10 yr	161/11 (6.8%)	172/7 (4.1%)	333/18 (5.4%)
1977	60/1	83/2	143/3
1978	65/1	92/0	157/1
1979	79/0	110/0	189/0
1980	52/0	101/1	153/1
1981	65/0	70/0	135/0
Total implanted 0–5 yr	321/2 (0.6%)	456/3 (0.7%)	777/5 (0.6%)
Total (0–10 yr)	482/13 (2.7%)	628/10 (1.6%)	1,110/23 (2.1%)

* One dialysis patient with aortic and mitral bioprostheses had PVD of both.

The yearly incidence of primary valve dysfunction is presented in Table III. Failure of bioprostheses seems to be a time-related process. There have been 11 primary failures in the 161 mitral bioprostheses implanted at least 5 years (an incidence of 6.8%) and 7 primary failures (4.1%) of the 172 aortic bioprostheses implanted before January 1977. The cumulative rate of failure f all prostheses implanted >5 years was 5.4%. In contras the incidence was extremely low in either site, less tha 1%, for bioprostheses implanted for <5 years.

On an actuarial basis the calculated probability freedom from primary valve dysfunction was 98% f isolated mitral and 96% for isolated aortic replacemen at 5 years and 79% for mitral and 91% for aortic at 1 years (Fig. 1). Although not yet of statistical differenc the data suggest that the failure rate of mitral biopro theses is higher than that of aortic bioprostheses.

Infective endocarditis in this patient group involve 8 patients with mitral valve replacements (2.1%), 7 wit aortic valve replacements (1.3%), and 4 with doub valve replacements (3.7%), an overall incidence of 19 1,001 cases or 1.9%. The actuarially calculated prob bility of freedom from endocarditis at 10 years with a bioprostheses was 90 ± 4%. This figure compares wit the probability of freedom from endocarditis at 10 yea with mechanical valve prostheses of 98 ± 1% at o hospital.

Figure 2 shows the actuarially calculated probabili of freedom from both infective endocarditis and pr mary valve dysfunction for isolated mitral and isolate aortic valve replacements. These probabilities were ± 2% for mitral and 96 ± 1% for aortic at 5 years and ± 7% and 84 ± 5%, respectively, at 10 years.

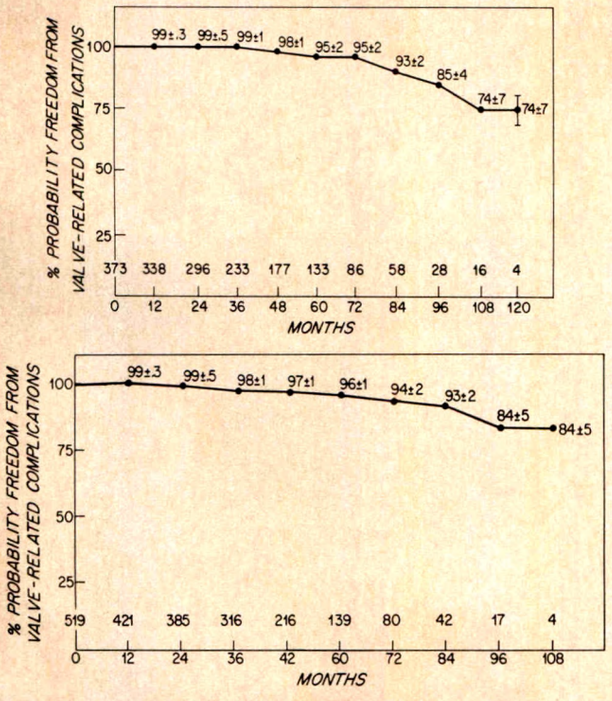


FIGURE 2. Actuarial probability, up to 120 months, of freedom from all local valve-related complications, including primary valve dysfunction and infective endocarditis for (**top**) 373 isolated mitral and (**bottom**) 519 isolated aortic bioprostheses at risk. **Figures above the time axis** denote numbers of patients at risk at each time interval. **Bars** denote value ± standard error of the mean.

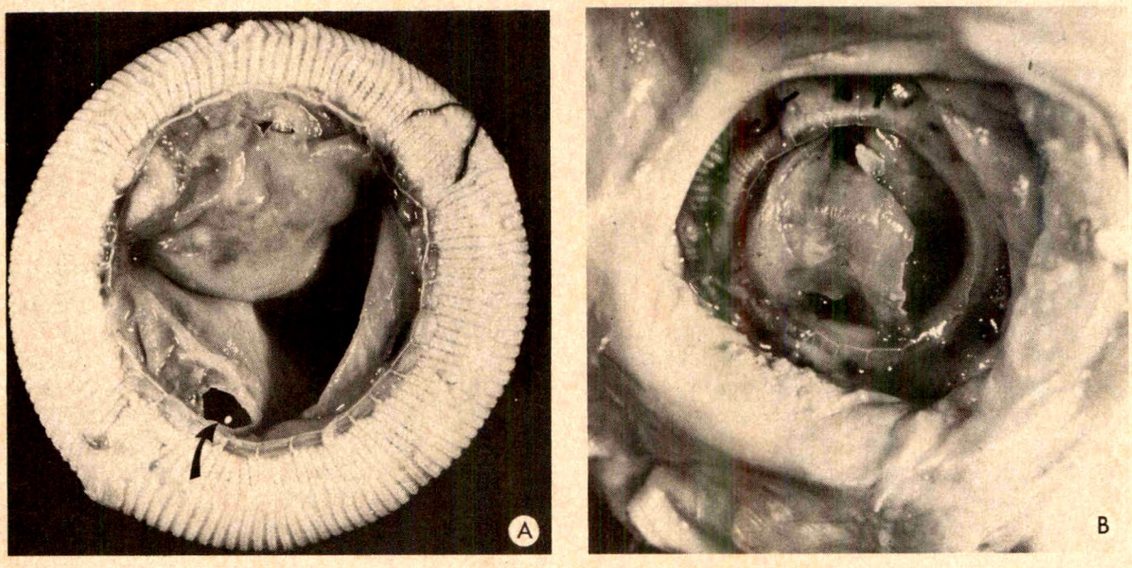
Morphologic correlations: Table IV summariz the clinicopathologic characterization of the 22 retrieve bioprosthetic valves. Four patients were operated because of primary cuspal tears of mitral prostheses the absence of calcification. These cuspal defects varie in size from minimal to complete cuspal dehiscence (Fi 3). All but 1 occurred as relatively early events, that i in the first 4 years after the original surgery.

Bioprosthetic dysfunction was commonly associate with cuspal calcific deposits (Fig. 4). The largest sing failure group was that of calcification-related tear These prostheses had substantial cuspal defects ass ciated with variable amounts of calcific material in th

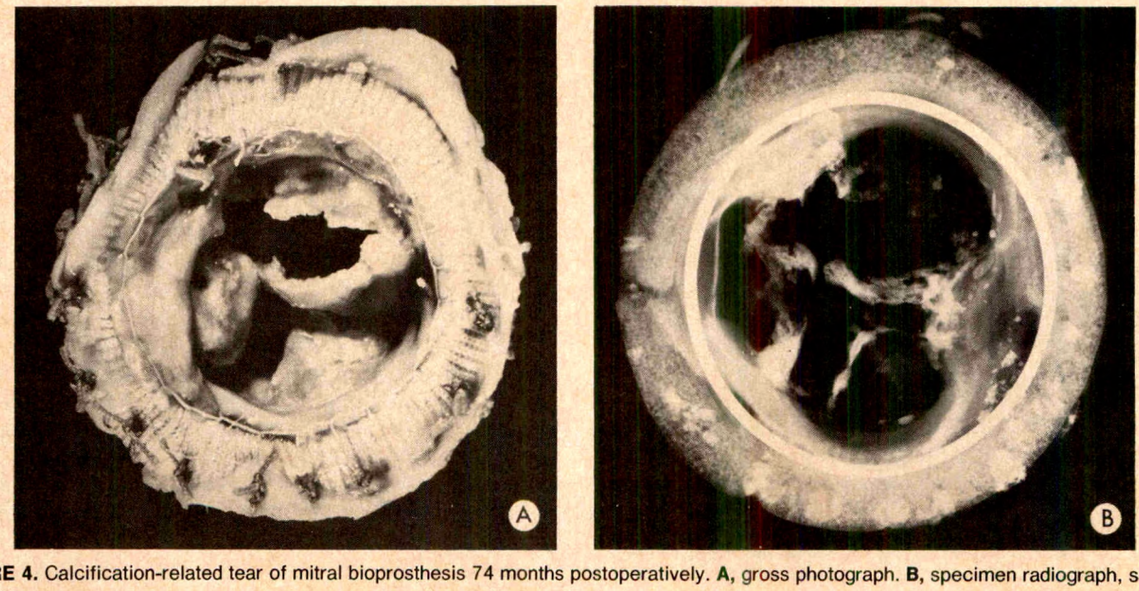
BLE IV Failed Valve Clinicomorphologic Data Summary

Clinicopathologic Process	n (M/A)	Duration (mo)		Range of Cuspal Defect	Range of Calcification
		Mean	Range		
Primary tear	4 (4/0)	44	12–84	+/+++	0
Calcification with tear	7 (4/3)	66	44–87	++/+++	+/+++
Stenosis	2 (1/1)	80	75–85	0	+/+++
Endocarditis	8* (3/5)	45	23–81	0/++	0/++
Thrombosis	1 (0/1)	12	. . .	0	0

One patient had endocarditis of both mitral and aortic valves.
- = mild; ++ = moderate; +++ = severe. A = aortic; M = mitral.



URE 3. Gross photographs showing range of primary cuspal tears in the absence of calcification. **A,** small perforation at base of cusp of mitral prosthesis after 84 months (**arrow**). **B,** complete dehiscence of cusp of mitral bioprosthesis. This patient was not reoperated on because of medical considerations and died 47 months after original surgery.



URE 4. Calcification-related tear of mitral bioprosthesis 74 months postoperatively. **A,** gross photograph. **B,** specimen radiograph, same orientation.

cusps (Fig. 4). Early calcification predominated in commissural regions of the cusps and was generally associated with severe collagen deterioration observed by light microscopy. Early calcific deposits were seen in both spongiosa and fibrosa of the porcine valve cusps. However, in many cases the cuspal architecture was so poorly preserved that precise anatomic localization was difficult.

Two patients had bioprosthetic stenosis in the absence of cuspal defects. One of these patients had a mitral valve prosthesis implanted for 85 months. Fine calcifications were revealed by radiography and histologic study at the cuspal commissures. Another patient presented with aortic bioprosthetic stenosis associated with considerable cuspal calcifications after 75 months of implantation.

Eight prosthetic valves with infective endocarditis were retrieved from 7 patients after 23 to 81 months. Bioprosthetic endocarditis often involved the va cusps themselves and was commonly quite destruc (Fig. 5A). The sewing ring was involved in several ca Deposition of calcium precipitates occurred seconda in the vegetations in most cases of endocarditis (5B), and generally predominated at the free cus edges (Fig. 5C). Ring abscesses occurred in 3 patie One patient died suddenly from subtotal stenosis o aortic prosthesis due to Streptococcus intermedius fection with superimposed thrombosis (Fig. 6). Th was extensive ring abscess demonstrably involving conduction system with 3° heart block and partial vular dehiscence.

The relation of duration of function to the prese of calcification is plotted in Figure 7. Calcification curred in infected valves independent of the lengt implantation. Noninfected valves removed before proximately 4 years were not calcified. Degenera

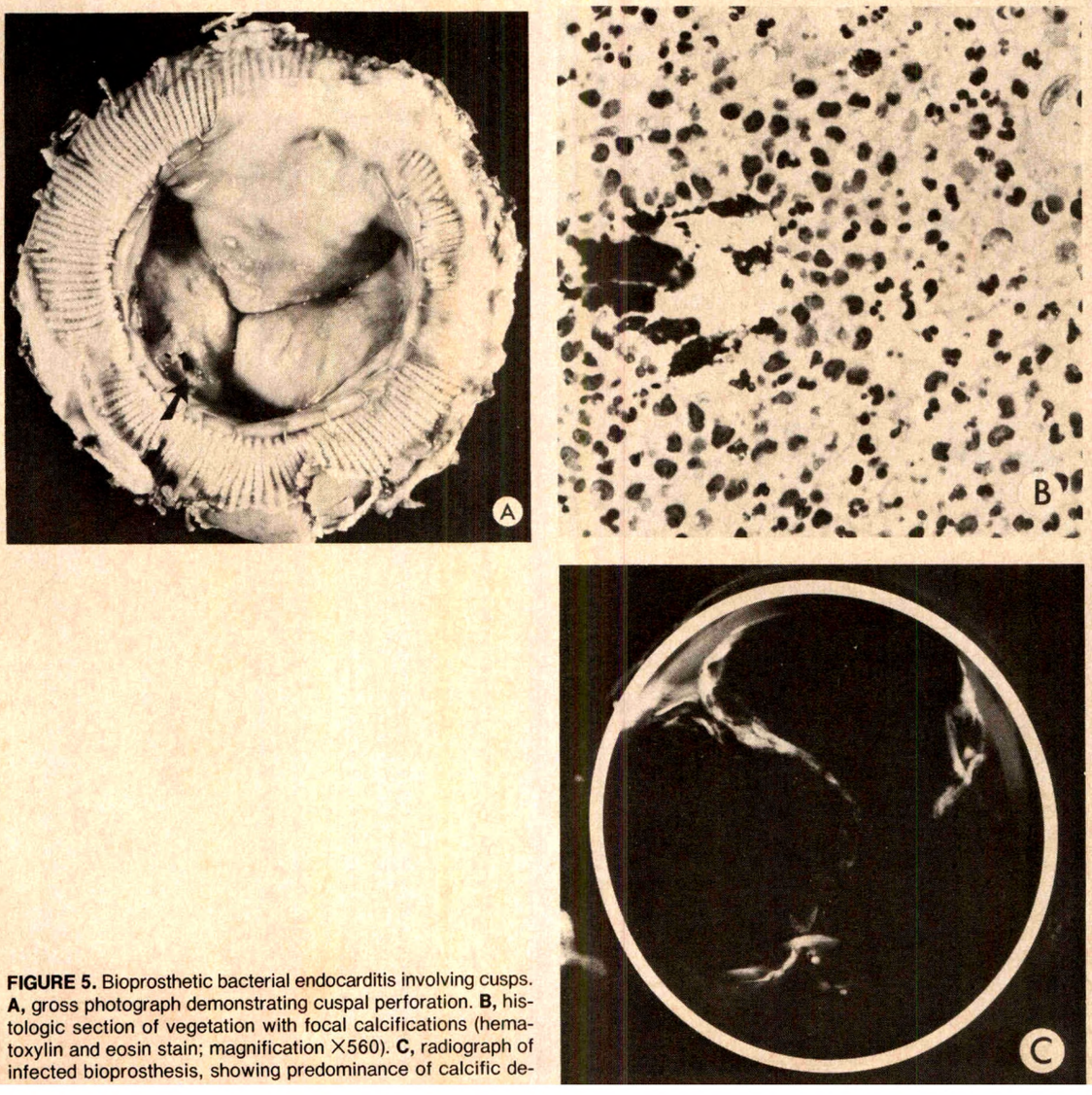


FIGURE 5. Bioprosthetic bacterial endocarditis involving cusps. **A,** gross photograph demonstrating cuspal perforation. **B,** histologic section of vegetation with focal calcifications (hematoxylin and eosin stain; magnification ×560). **C,** radiograph of infected bioprosthesis, showing predominance of calcific de-

cification became significant only in some individuals
l only after approximately 4 to 5 years of valve ser-
e.

Valvular thrombosis occurred in 1 valve analyzed.
rombotic deposits were predominantly on the out-
v surfaces of the prosthetic cusps (sinuses).

Discussion

Tissue valve replacements for diseased cardiac valves
e, as major advantages over mechanical prostheses,
w risk of thromboembolism, usually without anti-
gulation, and central flow characteristics. Failure of
chanical valve prostheses is often catastrophic, but
ny complications associated with biologic valve re-
cement are often slow in onset and therefore most
ients with such complications may successfully un-
go reoperation.

Time-dependent rate of failure: Mitral versus tic bioprostheses: This study describes the rate of
ical bioprosthetic valve dysfunction in a series of
10 such replacements in 1,001 adults over a 10-year
iod. Infective endocarditis was documented in 19
ients (1.9%). Primary valve dysfunction occurred in
aortic and 13 mitral valve replacements. In the lim-
l series with a minimum 60-month follow-up period,
re were 161 mitral and 172 aortic valve replacements.
e primary dysfunction rate was 6.8% for mitral
stheses and 4.1% for aortic. In 777 valves implanted
years the failure rate was <1%. The actuarial prob-
lity of valves being free of primary tissue dysfunction
6 months was 79 ± 7% for mitral valves and 91 ± 4%
aortic.

n the present study, porcine bioprosthetic valves in
mitral position failed more frequently than did those
in the aortic position. Several reasons for the disparity in failure rate between mitral and aortic prostheses are plausible. In studies of fatigue damage of glutaraldehyde-preserved porcine heart valve tissue, Broom[16] demonstrated that compressive flexure is more significant than tensile loading in its contribution to disruption of tissue integrity and potential long-term durability of bioprostheses. A recent biomechanical study suggests that such compressive stresses occur in vivo during valve opening and may explain degeneration of these valves.[17] The larger-sized mitral bioprostheses would be expected to have higher stresses than the aortic bioprosthesis.

However, the most plausible hypotheses that would account for a greater frequency of failure of mitral bioprostheses relative to aortic consider the closed valve. The diastolic pressure differential across the aortic prosthesis would be approximately 75 mm Hg compared with 115 mm Hg across the mitral prosthesis. Furthermore, the rate of closure is expected to be greater with a mitral compared with an aortic prosthesis.

The present study did not consider the possible late development of asymptomatic stenosis in patients whose condition was clinically stable, as suggested by Lipson et al[18] in a study of patients with mitral bioprostheses after extended postoperative intervals.

Primary disease of bioprosthetic heart valves: Logistical difficulties associated with auto- and allografts prompted the use of xenograft tissue for cardiac valve replacement. Study of formalin-preserved porcine

URE 6. Gross photograph illustrating fatal bioprosthetic bacterial
ocarditis (Streptococcus intermedius) with subtotal prosthetic
osis by vegetation with superimposed thrombus.

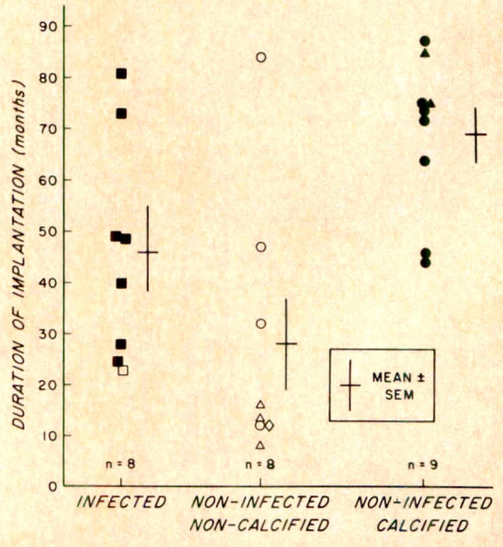


FIGURE 7. Relation of calcification to duration of implantation for infected and noninfected retrieved bioprosthetic heart valves. Calcification of infected valves is independent of postoperative interval. Calcification in noninfected bioprostheses is generally encountered only after approximately 4 years of service and only in some patients. **Open squares** = endocarditis, noncalcified; **closed squares** = endocarditis, calcified; **open circles** = cuspal tear, noncalcified; **closed circles** = cuspal tear, calcified; **open diamonds** = thrombosis; **open triangles** = paraprosthetic leak; **closed triangles** = stenosis with calcification. **All filled symbols** represent calcified valves. SEM = standard error of the mean.

aortic valves used as human aortic bioprostheses shows (up to 45 months after implantation) progressive changes involving loss of cells, collagen and elastin degeneration, ingrowth of host inflammatory cells, and cuspal rupture.[19,20] Available since 1970, glutaraldehyde-preserved flexible stent-mounted porcine aortic valve bioprostheses have gained wide acceptance in the replacement of diseased cardiac valves. Clinical performance has been satisfactory in most adult patients over an extended follow-up.[1–5] However, bioprostheses often fail relatively early in children,[6–10] probably because of age-related accelerated calcium metabolism.

Clinically significant valvular dysfunction is uncommon, and pathologic changes at the level of light microscopy are slight in the immediate postoperative period with glutaraldehyde-preserved porcine bioprostheses.[11,12] Nevertheless, scanning and transmission electron microscopic examination of unimplanted valves shows loss of endothelium and acid mucopolysaccharides during preimplantation processing.[13] Short-term (<1 to 2 months) changes after implantation consist of insudation of plasma proteins, penetration of erythrocytes into surface crevices, formation of a thin surface layer of fibrin, and deposition of macrophages, giant cells, and platelets. Long-term (>2 months) changes are time-related and consist of progressive disruption of collagen, erosion of the valve surfaces, formation of platelet aggregates, and accumulation of lipid. Although cuspal surfaces may become partially covered with endothelium, this event occurs late.[21]

Clinically significant late deterioration with or without thrombosis or calcification of these valves in the absence of antecedent endocarditis (primary tissue failure) is now encountered in some adult patients after 4 to 5 years of implantation.[1–5,22] In some cases, tearing and destruction or rigidity of valve cusps is associated with valvular thickening assessed by echocardiography.[23] In failed valves, characteristic time-related microscopic changes include fibrin deposition on and inflammation in the valve cusps, focal disruption of the cuspal fibrocollagenous matrix, and calcification.[13–15] Calcific deposits occur commonly in bioprostheses implanted in patients of all ages, but are more likely to become severe and clinically significant in children and young adults than in older patients. Although renal failure was present in several reported patients with early calcification, pertinent metabolic disorders are not identified in most patients with calcified prosthetic tissue valves. The 2 main sites of deposition of calcium phosphate in porcine valve bioprostheses are the connective tissue in the cusps, particularly in the spongiosa, and small thrombi on the surfaces.[14] An additional group of patients has gross disruption of cuspal integrity with tears in the absence of calcific deposits. Such defects may occur at any time after surgery, but usually occur within the first few years and are often associated with changes in collagen structure which account for their origin.[15]

Clinicopathologic failure modes: The morphologic observations we report are consistent with those of previous studies described herein and emphasize that

dysfunction of porcine bioprostheses takes mul
major clinicopathologic forms. Primary tissue fa
may occur relatively early in the absence of calcific
and is due to disruption of the fibrocollagenous sup
network of the valve. These failures take the for
commissural tearing or basilar linear perforations (
I and II lesions described by Ishihara et al[15]). O
patients with such tears had mitral bioprostheses

The most frequent mode of primary valvular
function in our study was calcification-associated
in the absence of endocarditis. Early deposits wer
calized at the commissures. More severe cases
generalized calcifications. Tears in calcified valves
generally large. All such valves were in place for
months (mean 66). One mitral and 1 aortic prostl
had thickening and stiffening of the valve cusps wit
perforation or tear. These 2 patients had a clinical
ture compatible with stenosis and the valves had ca
deposits.

Bioprosthetic infective endocarditis: As wi
mechanical cardiac valve prosthesis, infection
porcine bioprosthesis is a serious complication.
Although our incidence of endocarditis is lower
mechanical prostheses than with bioprostheses, ot
report a similar incidence (approximately 1%)
mortality rate (approximately 33%) for infection
bioprostheses and mechanical prostheses.[24] With
types of prostheses, aortic valve infections are gene
more common than mitral. With mechanical prosth
infection is initiated at the host tissue/prosthesis se
ring junction. Although sewing ring infection may o
with bioprostheses, infection often solely involves
cuspal tissue.[25] Medical therapy may thus sterilize s
of these infections.[24] However, infection of por
bioprostheses in contrast to mechanical prostheses
involve and destroy the prosthetic material it
leading in some cases to stiffening, calcification,
perforation of the valve cusps.[25,26] Although it has
suggested that valve ring abscesses and perivalv
leaks are uncommon in porcine valve infection, t
complications certainly do occur and may have the s
catastrophic consequences as does mechanical p
thetic valve endocarditis.

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Comparison of Late Degenerative Changes in Porcine Bioprostheses in the Mitral and Aortic Valve Position in the Same Patient

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Porcine bioprostheses implanted in both the mitral and aortic valve positions simultaneously in 5 patients aged 20 to 61 years (mean 45) were reexamined 18 to 107 months (mean 51) later. In 4 patients, the degenerative changes were distinctly more severe in the bioprostheses in the mitral than in the aortic valve position.

Many reports have described degenerative changes in porcine bioprostheses implanted in either the mitral or aortic valve position.[1–5] None, however, have described morphologic alterations in bioprostheses in both positions in the same patient. The latter situation, of course, allows one bioprosthesis to serve as a control for the other. This report summarizes clinicopathologic findings in 5 patients in whom porcine aortic bioprostheses had been implanted 18 to 107 months earlier in both mitral and aortic valve positions.

Patients Studied

Clinical findings: Clinical and morphologic findings in the 5 patients are summarized in Table I. At the time of initial double valve replacement, the 5 patients (4 men) ranged in age from 20 to 61 years (mean 45). Late postoperatively, chronic congestive heart failure developed in 4 (all but Patient 1), and 3 of them (Patients 2, 3, and 5 [Table I]) had their malfunctioning bioprostheses in both the mitral and aortic valve positions excised, and replaced with mechanical prostheses. The remaining patient (Case 4), who had chronic congestive heart failure, died from complications of primary biliary cirrhosis before her malfunctioning bioprosthesis in the mitral position could be replaced. The 1 patient (Case 1) without clinical evidence of congestive cardiac failure c prosthetic valve dysfunction died from complications of ha bitual alcoholism.

Morphologic findings: The 10 bioprostheses are illus trated in Figures 1 to 5. Each cusp was thicker than norma and *cuspal mobility* appeared distinctly diminished in bioprostheses (3 mitral and 2 aortic). Each of these bioprostheses appeared on visual inspection to have som degree of obstruction, and catheterization in 2 patients (Case 2 and 3) confirmed bioprosthetic stenosis in both mitral an aortic positions.

Calcific deposits were present in 1 or more cusps in all 1 bioprostheses. In 4 of the 5 patients, the calcific deposits wer clearly larger on the cusps of the bioprostheses in the mitra position than on the cusps in the aortic position. In 2 patient (Cases 3 and 5) *cuspal tears* were present, and they also in volved only the bioprostheses in the mitral positior Bioprosthetic *thrombus* was present only in the patient (Cas 2) with infective endocarditis.

Of the 2 patients in whom the bioprostheses had been i place for <2 years, 1 (Patient 1) had mild degenerativ changes in both valves, those in the aortic position bein slightly more marked. The other patient (Case 2) whos bioprosthetic valves deteriorated rapidly had clinical an morphologic evidence of infective endocarditis; vegetations present on both bioprostheses, contained fungi and bacteria but no inflammatory cells, cuspal tears, or perforations.

Discussion

Examination of the bioprostheses located in bot mitral and aortic valve positions clearly demonstrate in 4 of the 5 patients greater degeneration of th bioprosthetic cusps located in the mitral valve positio than in those in the aortic valve position. The reason

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TABLE I Clinical and Morphologic Data in the 5 Patients With Porcine Bioprostheses in Both the Mitral and Aortic Valve Positions

Case	Age Bioprosthesis Implanted (yr)	Duration (mo) Bioprosthesis in Place	Sex	AF	TC (mg/dl)	Bioprosthetic Dysfunction by Auscultation				Hemodynamic Data* (mm Hg)				Died	Ca^{++} (0–4+) on Bioprosthesis	
						MS	MR (0–4+)	AS	AR (0–4+)	LV (s/d)	SA s/d	LV-Ao (psg)	PAW-LV (mdg)		MV	AV
1	40	18	M	+	98	0	0	0	0	–	100/70†	–	–	+	1+	2+
2	61	20	M	+	149	+	4+	+	2+	118/8	80/55	38	6	0	3+	2+
3	20	48	M	0	183	+	4+	+	0	130/15	96/70	34	15	0	3+	1+
4	54	60	F	+	259	+	+	0	0	–	100/90†	–	–	+	4+	2+
5	48	107	M	0	160	0	4+	0	0	107/12	96/57	11	0	0	2+	1+

* Obtained just before replacement of the bioprostheses.
† Indirect.
AF = atrial fibrillation; Ao = aorta; AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; Ca^{++} = calcium; CHF = congestive heart failure; LV = left ventricular pressure; mdg = mean diastolic gradient; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; PAW = pulmonary arterial wedge; psg = peak systolic gradient; s/d = peak systole/end-diastole; TC = total serum cholesterol; – = not done; 0 = absent; + = present.

for the more extensive degeneration of the bioprostheses in the mitral position are unclear but at least 4 factors need consideration.

1. The closing pressure on the bioprosthesis in the mitral position is higher than that on the bioprosthesis in the aortic position.

2. The pressure difference across the closed bioprosthesis in the mitral position is far higher than that across the closed bioprosthesis in the aortic position. The higher the pressure difference across the closed bioprosthesis, the greater the tensile stress on the cusps.[6]

3. The presence of a bioprosthesis composed of a semilunar valve in the atrioventricular valve position

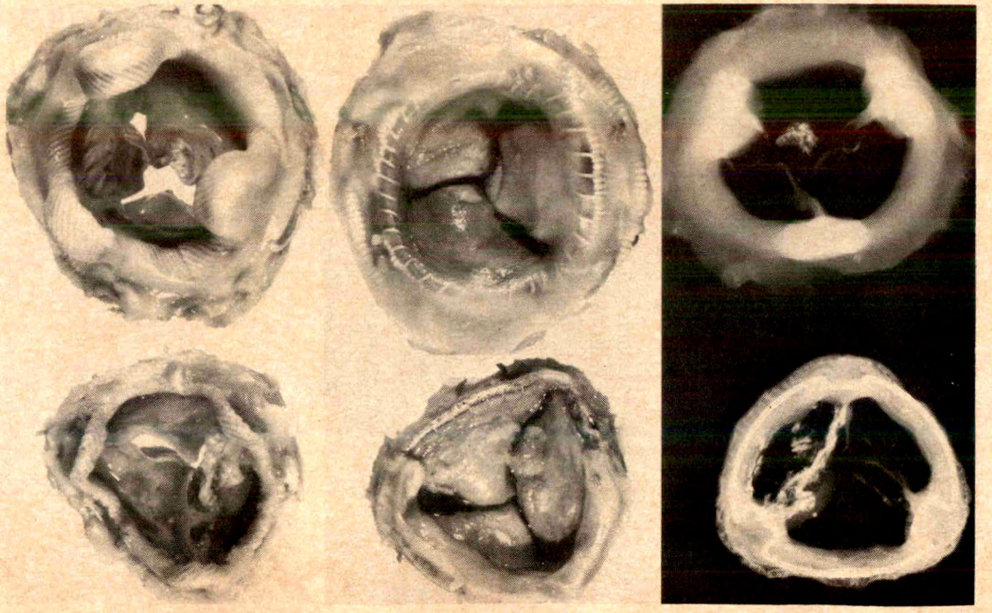

FIGURE 1. Patient 1 (Table I). Excised porcine bioprostheses from the mitral (**left**) and aortic (**right**) valve positions. **Top,** radiographs showing a minute calcific deposit in 1 of 3 cusps of the bioprosthesis in the mitral position and more calcium in 1 of the 3 cusps in the bioprosthesis in the aortic position. **Middle,** views of mitral-position bioprosthesis from the atrial aspect and of the aortic-position bioprosthesis from the ventricular position. **Bottom,** view of the mitral-position bioprosthesis from the ventricular aspect and of the aortic-position bioprosthesis from the aortic aspect.

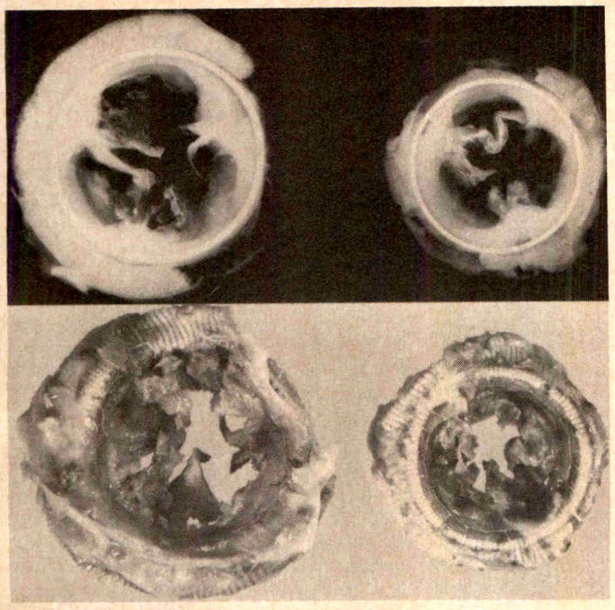

FIGURE 2. Patient 2. **Top,** radiographs showing extensive calcific deposits in all 3 cusps of the bioprostheses in both mitral (**left**) and aortic (**right**) valve positions. **Bottom,** view of the mitral-position bioprosthesis from the atrial aspect and of the aortic-position bioprosthesis from the ventricular aspect. There is considerable destruction of cusps of both bioprostheses caused at least in part by infective endocarditis. Sections had been removed previously for histologic studies.

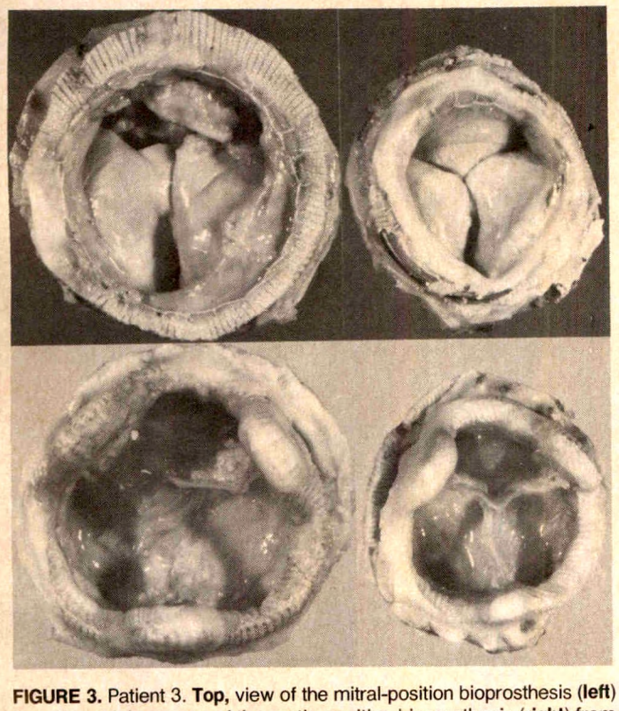

FIGURE 3. Patient 3. **Top,** view of the mitral-position bioprosthesis (**left**) from the atrial aspect and the aortic-position bioprosthesis (**right**) from the ventricular position. **Bottom,** view of the mitral-position bioprosthesis (**left**) from the ventricular aspect showing extensive calcific deposits in all 3 cusps. The aortic-position bioprosthesis viewed from the aortic aspect is on the right.

may prevent equal distribution of the left ventricular systolic pressure on each of the 3 bioprosthetic cusps (Fig. 6), whereas the aortic diastolic pressure is probably equally distributed on each of the 3 aortic valve cusps.

4. Sinus rhythm theoretically causes more work for the cusps of a mitral valve than for the cusps of an aortic valve, as atrial contraction partly reopens the valve. In contrast, the aortic valve opens only once during each cardiac cycle. The "double movement" of mitral opening when the mitral valve consists of an

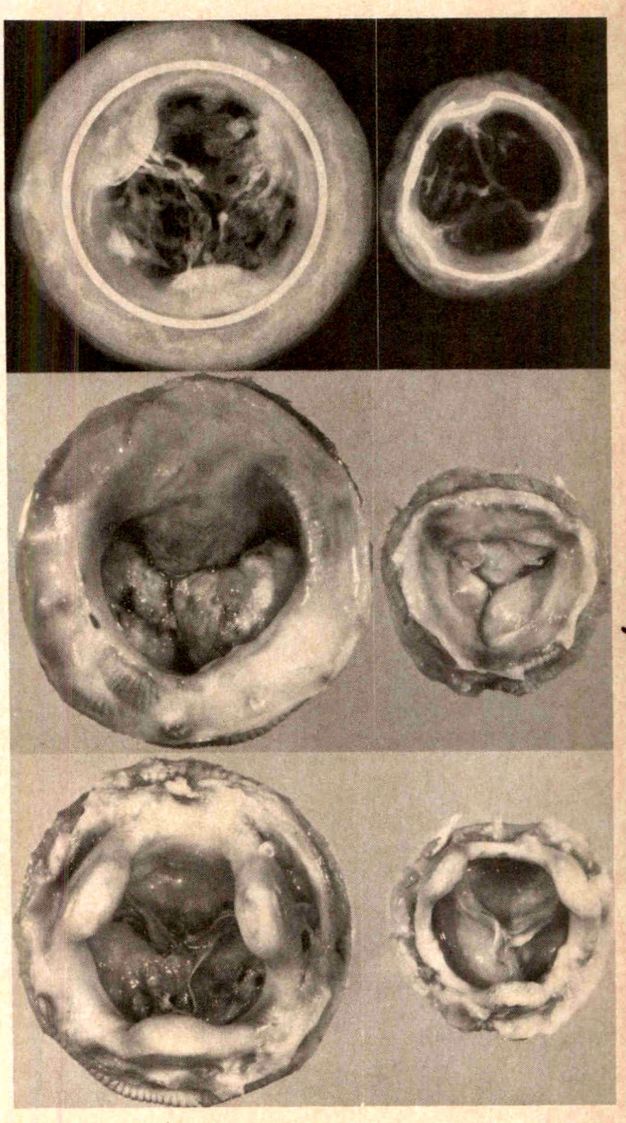

FIGURE 4. Patient 4. **Top,** radiographs showing extensive calcific deposits in all 3 cusps of the bioprosthesis in the mitral position (**left**) and much smaller amounts of calcium in the aortic-position bioprosthesis (**right**). **Middle,** view of the mitral-position bioprosthesis (**left**) from the atrial aspect and of the aortic-position bioprosthesis (**right**) from the ventricular aspect. **Bottom,** view of the mitral-position bioprosthesis (**left**) from the ventricular aspect and of the aortic-position bioprosthesis (**right**) from the aortic aspect.

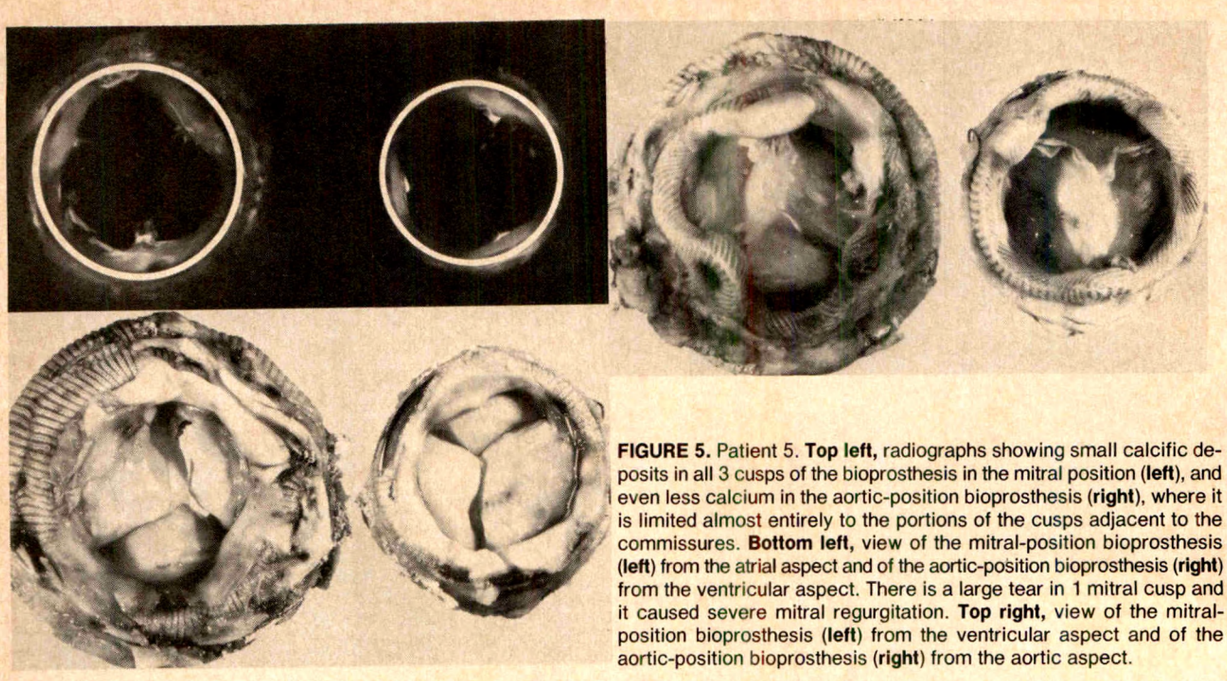

FIGURE 5. Patient 5. **Top left,** radiographs showing small calcific deposits in all 3 cusps of the bioprosthesis in the mitral position (**left**), and even less calcium in the aortic-position bioprosthesis (**right**), where it is limited almost entirely to the portions of the cusps adjacent to the commissures. **Bottom left,** view of the mitral-position bioprosthesis (**left**) from the atrial aspect and of the aortic-position bioprosthesis (**right**) from the ventricular aspect. There is a large tear in 1 mitral cusp and it caused severe mitral regurgitation. **Top right,** view of the mitral-position bioprosthesis (**left**) from the ventricular aspect and of the aortic-position bioprosthesis (**right**) from the aortic aspect.

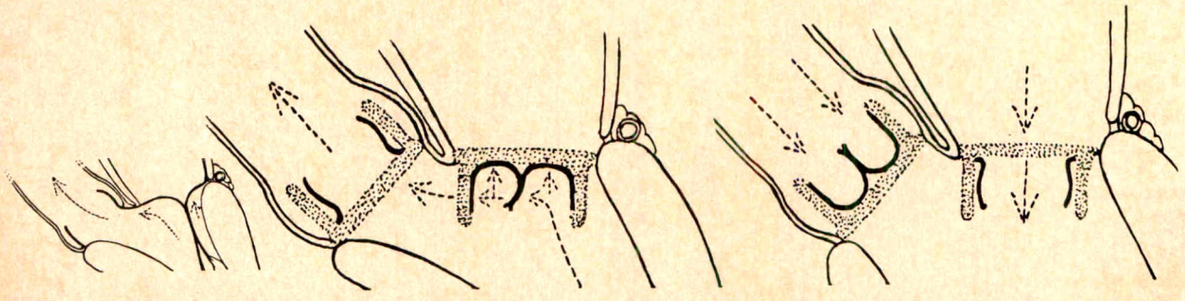

FIGURE 6. Diagrams of normal mitral valve (**left**) as it might appear during ventricular systole, and of a heart containing bioprostheses in both the mitral and aortic valve positions (**center and right**). With a semilunar valve in the mitral position, left ventricular systolic pressure does not easily "glide" from the ventricular aspect of the cusps to the aorta as it does with the native anterior mitral leaflet (**left**).

aortic valve bioprosthesis, theoretically causes additional bending of the cusps near the commissures. This local concentration of deformation on the cusps near the commissures may accelerate fatigue fractures of the collagen bundles.[7]

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Phonocardiographic Findings in Patients With Normally Functioning Ionescu-Shiley Prostheses

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Phonocardiographic findings are reported in 19 patients with normally functioning Ionescu-Shiley prostheses in the mitral or aortic position. Opening clicks were recorded in all 8 patients with mitral prostheses at a mean second heart sound (A2) to opening click interval of 94 ms. In 9 subjects, apical systolic murmurs were found. All 11 patients with the prosthesis in the aortic position had systolic ejection murmurs. Opening clicks were observed in 8 patients with a mean Q wave to opening click interval of 125 ms; closing clicks were found in 9 of 11. No diastolic murmurs occurred in this group. These acoustic characteristics serve as a reference source for the noninvasive evaluation of the bovine pericardial prosthesis.

In the follow-up of a group of clinically stable patients who had received the Ionescu-Shiley pericardial xenograft heart valve, we sought to document the murmurs and clicks heard during auscultation.

Methods

Phonocardiograms were recorded in 19 patients aged 42 to 63 years who had undergone valve replacement with the Ionescu-Shiley prosthesis. Eight had the prostheses implanted in the mitral position and 11 in the aortic position. Table I summarizes the diagnostic findings at the time of cardiac catheterization before surgical intervention, as well as the lapse of time from operation to the time of the study (range 1 to 16 months, mean 6).

The records were obtained with a commercially available Electronics for Medicine VR12 simultrace recorder, and an Irex phonorecorder. Leatham-type microphones were applied in all cases. Phonocardiograms were systematically evaluated for clicks, murmurs, and other transient sounds. The following measurements were made on the recordings from subjects with aortic prostheses: Q wave to opening click interval and relationship of closing click to dicrotic notch on the simultaneously recorded external carotid arterial pulse tracing. For those with mitral prostheses, the second heart sound to opening click interval was measured.

Results

All 8 patients with the Ionescu-Shiley pericardial xenograft in the mitral position had a loud sound after the second heart sound (Fig. 1). Appropriate filtering indicated that this sound had high frequency characteristics (Fig. 2). Simultaneous left ventricular apexcardiography disclosed that the sound was inscribed concurrent with the O point, suggesting that it was associated with prosthetic opening (Fig. 3). The second heart sound-opening click interval ranged from 80 to 120 ms, with a mean of 94 (Table I). Seven of these subjects also had a change in the quality of the first heart sound, which acquired closing click-like characteristics. The mean Q wave to closing sound interval ranged from 70 to 100 ms with a mean of 80 (Table I). In 7 of 8 patients, low amplitude, high frequency murmurs were recorded. In 3 of the subjects, the murmurs were ejection in quality; the other 4 were holosystolic. These murmurs were heard and recorded best at the mitral and pulmonary areas. In 2 of the patients, early diastolic murmurs were recorded. One of these patients had aortic insufficiency and the other had severe pulmonary hypertension.

In 9 of the 11 patients with aortic prostheses, we found loud high frequency sounds preceding the dicrotic notch of the carotid arterial pulse by a mean interval of 16 ms. In 8 of these subjects, lower amplitude, high frequency sounds were recorded after the Q wave by a mean interval of 125 ms (Fig. 4 and Table I). Early systolic ejection murmurs were heard and recorded in all 11 patients in this group; the murmurs were loudest in the pulmonary and tricuspid areas. No diastolic murmurs were recorded in this group of patients.

Discussion

Ionescu et al[1,2] reported the development of heart murmurs in 3.9% of their large series after implantation of the pericardial valve prosthesis. Phonocardiographic study in subjects with this xenograft should be useful since such recording has aided in the detection of porcine valve malfunction through the development of new clicks, changes in the spectral frequency of the closing sound,[3] and new murmurs.[4,5]

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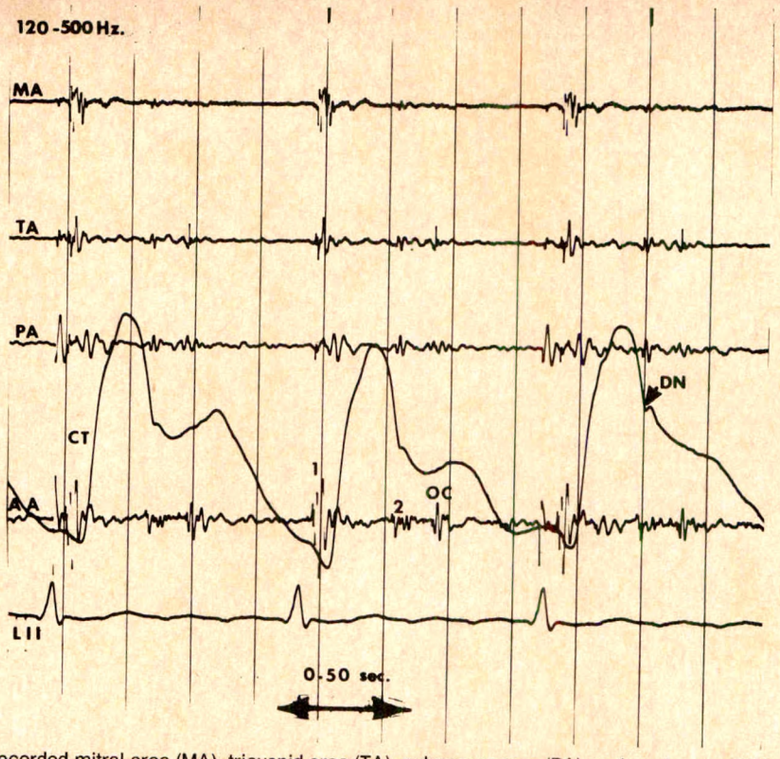

FIGURE 1. Simultaneously recorded mitral area (MA), tricuspid area (TA), pulmonary area (PA), and aortic area (AA), medium frequency phonocardiograms, external carotid pulse tracing (CT), and lead II (LII) of the electrocardiogram in a patient with an Ionescu-Shiley mitral valve prosthesis. Note the prominent opening click (OC) which follows the second heart sound. DN = dicrotic notch.

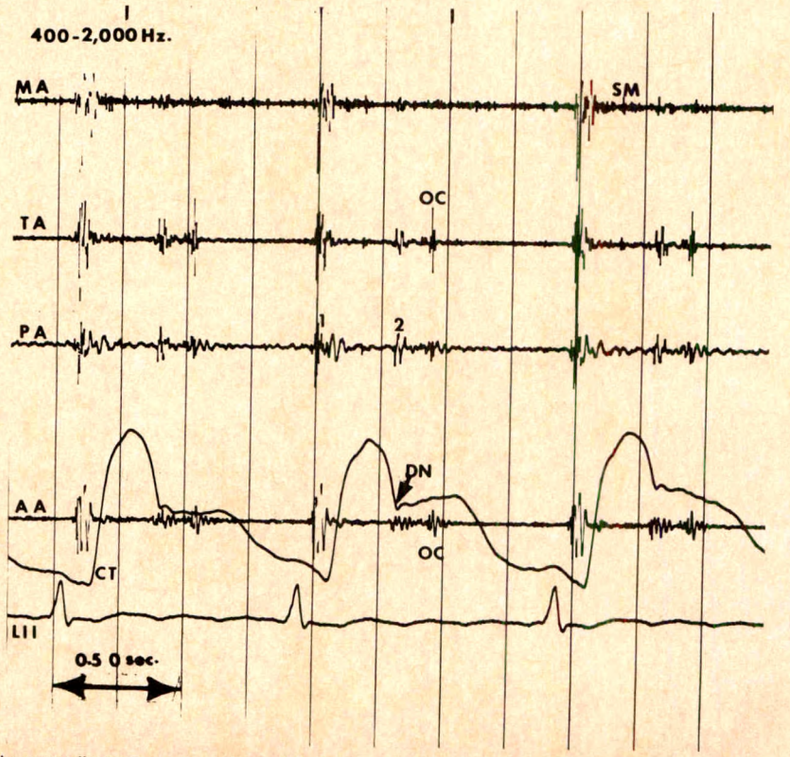

FIGURE 2. High frequency phonocardiograms, external carotid pulse tracing, and lead II of electrocardiogram in a patient with an Ionescu-Shiley mitral valve prosthesis. Note the increased intensity of the first heart sound and the well-recorded high frequency opening click. SM = systolic murmur; other abbreviations as in Figure 1.

TABLE I Study Group

Patient	Age (yr) & Sex	Diagnosis	Interval Between Valve Replacement and Phonocardiography (mo)	Opening Click A2-OC* (ms)	Closing Click Q-CC† (ms)	Systolic Murmur	Diastolic Murmur
			Mitral Prosthesis				
1	58F	MS	1	115	80	Holosystolic	0
2	41F	MR, AR	2	90	80	Holosystolic	0
3	55F	MR, AR, TR	2	80	80	Ejection	0
4	54F	MS	3	90	100	Ejection	Aortic
5	58F	MS	8	80	0	Ejection	0
6	56F	MS	8	80	70	0	Pulmonary
7	52F	MS	11	100	70	Holosystolic	0
8	63F	MS, AS, AR	12	120	80	Holosystolic	0
			Aortic Prosthesis				
				Q-OC‡ (ms)	C-DN§ (ms)		
1	68M	AS	2	140	20	Ejection	0
2	68F	AS	3	. . .	. . .	Ejection	0
3	50F	AR	3	160	30	Ejection	0
4	59F	AS, AR	4	140	10	Ejection	0
5	66F	AS	5	. . .	. . .	Ejection	0
6	64M	AS	6	120	10	Ejection	0
7	42F	Starr-Edwards valve malfunction	7	80	30	Ejection	0
8	56M	AS, MR, TR	7	120	20	Ejection	0
9	63M	AS	8	120	10	Ejection	0
10	63M	AS	9	120	Simultaneous	Ejection	0
11	61M	Bjork-Shiley valve malfunction	16	. . .	20	Ejection	0

AR = aortic regurgitation; AS = aortic stenosis; MR = mitral regurgitation; MS = mitral stenosis; TR = tricuspid regurgitation.
* Second heart sound (A2) to opening click (OC) interval.
† Q wave to closing click (CC) interval.
‡ Q wave to opening click interval.
§ Closing click to dicrotic notch (DN) interval.

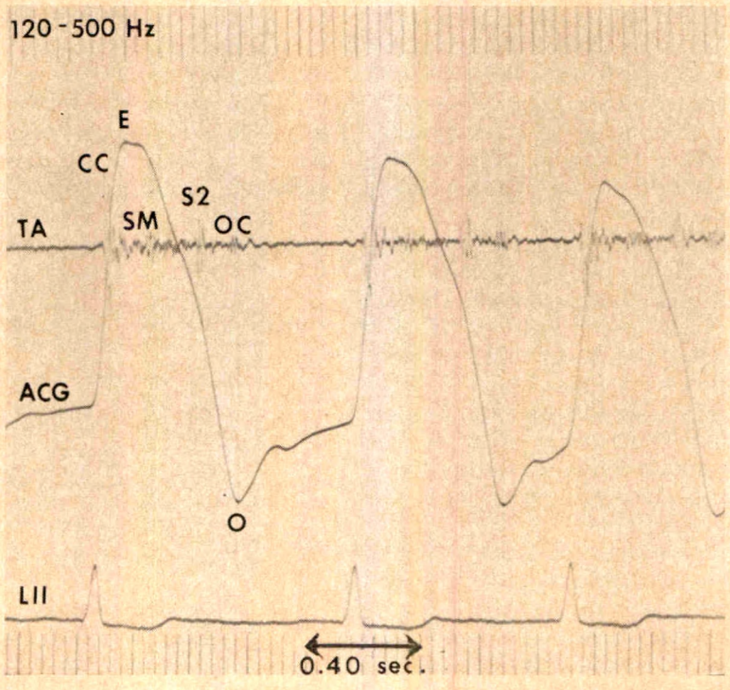

FIGURE 3. Simultaneously recorded tricuspid area (TA), phonocardiogram, apexcardiogram (ACG), and lead II (LII) of electrocardiogram in a patient with an Ionescu-Shiley mitral valve prosthesis. Note that the opening click (OC) is inscribed in conjunction with the apex-cardiographic O point. CC = closing click.

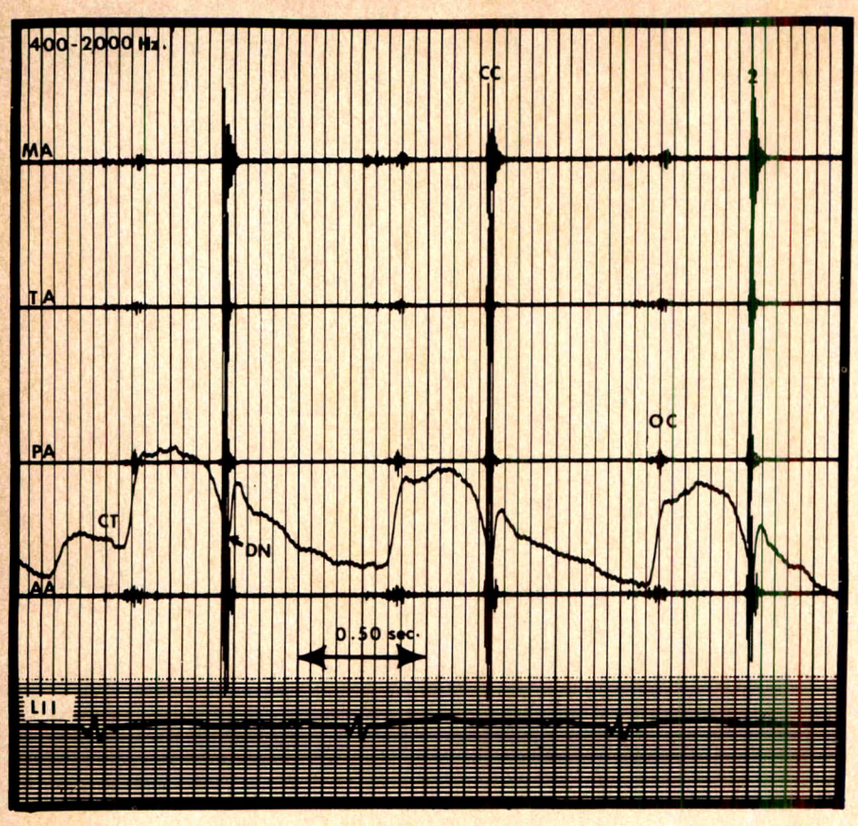

FIGURE 4. Phonocardiograms, external carotid pulse tracing, and lead II of electrocardiogram from a patient with an Ionescu-Shiley prosthesis in the aortic position. Note the high amplitude, high frequency closing click inscribed in conjunction with the dicrotic notch. A low amplitude, high frequency opening click follows the first heart sound. Abbreviations as in Figure 1.

Soft opening sounds have been reported occasionally in patients with a porcine heterograft in the mitral position.[4] The apparent rarity of such sounds, however, would mitigate utility of the second heart sound to mitral valve opening interval, which has been proven valuable in the detection of mechanical valve obstruction or paravalvular leak.[6–9] In particular, lengthening or shortening of the second heart sound to mitral valve opening indicates valvular obstruction and paravalvular leak, respectively, in this setting.[6,9]

In contradistinction to the porcine mitral xenograft, we found that the Ionescu-Shiley pericardial valve in the mitral position uniformly produces an opening click. It is of interest that the mean second heart sound to opening sound interval was 94 ms because this value correlates well with opening click times cited for the normally functioning mechanical prosthesis in the mitral position.[6] Further study is needed in order to determine whether or not alteration of this interval has the same clinical significance for the detection of Ionescu-Shiley mitral valve dysfunction.

In the series reported by Ionescu and Tandon,[1] 10.5% of the patients with the pericardial xenograft in the aortic position had early diastolic murmurs shown to be secondary to paravalvular leak. None of our subjects had suspected aortic leaks, yet all had systolic ejection murmurs. These murmurs can be attributed to turbulent flow through the prosthesis. Opening clicks were recorded in 8 of these patients with Ionescu-Shiley aortic valve prostheses. We found a mean Q wave to opening sound interval of 125 ms in our study group; this accords well with aortic opening click times in groups of patients with mechanical prostheses.[8,9] Attenuation or disappearance of this aortic opening click in subjects with the Ionescu-Shiley valve may serve to indicate valve failure in long-term serial study.

In conclusion, the Ionescu-Shiley valve xenograft manifests acoustic qualities which resemble, in part, those of mechanical prostheses. In contrast to porcine valves, the opening sounds are frequent and may provide a basis for simple noninvasive follow-up by auscultation and phonocardiography.

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M-Mode and 2-Dimensional Echocardiographic Characteristics of the Ionescu-Shiley Valve in the Mitral and Aortic Positions

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Using M-mode and 2-dimensional (2-D) echocardiography, ultrasonic features of the Ionescu-Shiley valve were characterized. A number 23 prosthesis was placed in a saline-filled chamber and subjected to pulsatile flow. Production of a linear tear at the base of a cusp resulted in coarse fluttering in the open position, and there was a reduction in the anterior cusp slope. Partial detachment of a cusp from its stent produced high-amplitude low-frequency fluttering during ejection. Alteration of transducer position eliminated the abnormal echoes. Fourteen patients with aortic and 11 with mitral prostheses were studied. There was a close approximation of echographically determined values for the bare stent internal diameter, cusp excursion, and valve orifice diameter compared with the manufacturer's specifications. Random punctiform echoes were noted when the cusps opened. Cusp echoes were superimposed on stent echoes in 21% of patients, and a third cusp was detected in 29%. Two-dimensional echocardiograms of good quality were recorded in the vast majority of subjects. Cusp echoes were smooth and had a consistent motion in both the short and longitudinal axis. Multiple transducer positions were required to delineate prosthetic components with optimal clarity. It is concluded that (1) M-mode and 2-D echocardiography is useful in assessing Ionescu-Shiley valve function, (2) in vitro valve tears or detachment produces characteristic cusp fluttering, (3) careful attention to transducer positions is necessary to record high-quality valve images, and (4) these findings represent a data base for the longitudinal follow-up study of patients with the Ionescu-Shiley valve.

The Ionescu-Shiley pericardial xenograft valve has been shown to have long durability and a low incidence of valve dysfunction and thromboembolism with adequate preservation of the tissue structure in up to 67 months of follow-up.[1–6] The symmetry of its design permits simultaneous cuspal motion and smaller transvalvular gradients than with most porcine heterograft valves. This report describes the echocardiographic features of the normally functioning Ionescu-Shiley pericardial xenograft in vitro and in vivo in both the mitral and aortic positions. We used methods previously employed for ultrasonic study of other bioprostheses.[7–15]

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Methods

In vitro study: M-mode and 2-D echocardiograms were obtained from a number 23 Ionescu-Shiley valve before and after it was sewn to an especially constructed nylon conduit. The inflow area of the conduit and valve was connected to the outlet of a commercially available centrifugal pump (DIAL model D-75) which was electronically modified to deliver hemisinusoidal pulsatile flow of saline solution with stroke volumes of 50 to 100 ml. The outflow portion of the conduit was connected to a distensible rubber reservoir, which produced a continuous distal pressure regulated by partly clamping its outlet (Fig. 1). Two-dimensional echocardiograms were obtained with (1) a Smith-Kline EkoSector I (model 2022), (2) a single crystal mechanical transducer (2.25 mHz) swept through a 30° sector, and (3) an Irex phased array sector scanner. M-mode echocardiograms were obtained with Smith-Kline and Irex models.

The images were recorded in a Sanyo VT video cassette and individual frames were photographed with a Polaroid® camera. M-mode echocardiograms were obtained with the ultrasonic beam intersecting the valve at 30° to 40° from the hor-

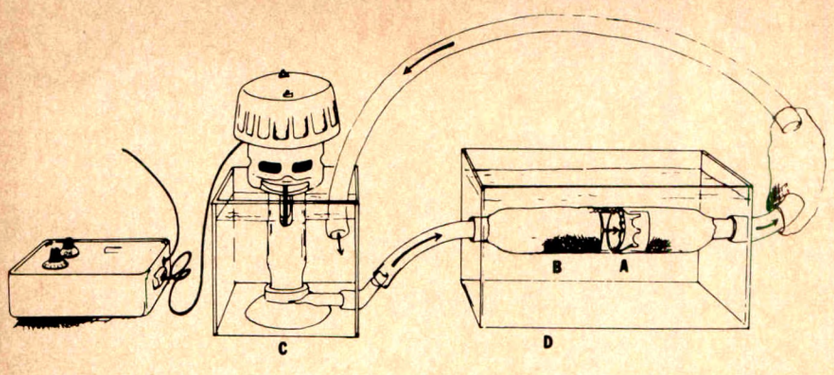

FIGURE 1. Chamber for in vitro echocardiographic studies of Ionescu-Shiley valve. **A,** Ionescu-Shiley valve, size 23; **B,** nylon conduit; **C,** pump; **D,** saline chamber.

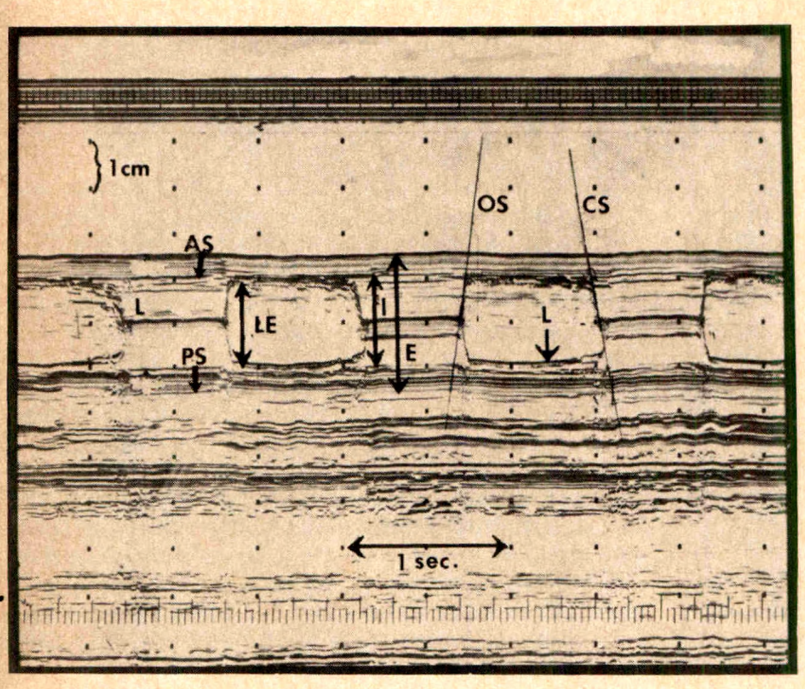

FIGURE 2. M-mode echocardiogram of the Ionescu-Shiley prosthesis sutured to a nylon conduit showing the various structures and measurements during pulsatile flow. AS = anterior stent; CS = closing slope; E = external stent diameter; I = internal stent diameter; L = cusp; LE = cusp excursion; OS = opening slope; PS = posterior stent.

izontal and sagittal planes. Two-dimensional echocardiograms in the longitudinal and transverse planes were obtained with the same approach. This examination was repeated after rendering the valve insufficient by (1) producing a 6 mm linear tear in the base of 1 of the cusps, and (2) detaching a single cusp from 1 of its 2 stents.

In vivo study: Twenty-five patients, aged 41 to 68 years, were studied 1 to 12 months after surgery: 14 had aortic and 11 had mitral valve replacement. None had clinical evidence of bioprosthetic dysfunction.

Two-dimensional echocardiograms were obtained in 11 patients, with the prosthetic valve in the aortic position in 6 and in the mitral position in 5. To record optimal echoes from the prostheses, multiple transducer positions were used in addition to the standard acoustic window.[15–17] In general, the cusps required selective setting adjustment, as reported with other bioprostheses.[9,11,12] High-gain dampening and relatively low reject were found more useful for this purpose. The approach described by Schapira et al[14] was used in the 2-D studies. Examinations were performed with the patient in the left lateral position. All measurements represent the mean of 3 consecutive estimations. In the aortic position measurements included the diameter of the leading edges of the stent, internal and external diameter of the stent, internal/external stent diameter ratio, and cusp excursion. In the mitral position similar measurements were made in addition to measurements of the initial diastolic slope of the anterior cusp and stent, systolic anterior excursion of the stent, and left ventricular outflow tract dimension.

The opening motion of the Ionescu-Shiley valve in the aortic position produced a faint, steep, and discontinuous linear echo which was difficult to record. Two-dimensional measurements in both positions included cusp thickness and stent diameter. The following qualitative characteristics established for the porcine prosthesis by other investigators,[13,14,17] were assessed in this study: consistency of cusp motion, changes of prosthetic axis in the longitudinal plane throughout the cycle, concordancy of prosthetic and myocardial motion, quality of echoes arising from the cusps and stents (smoothness), and left ventricular wall motion.

TABLE I M-Mode Measurements for the Ionescu-Shiley Prosthesis in the Aortic Position

Patients	Valve Size*	Diameter of Leading Edges of Stents (mm)	Internal Diameter of Stents (mm)	External Diameter of Stents (mm)	Internal/ External Diameter Ratio	Cusp Excursion (mm)
DP	23	28	18	23	0.78	. . .
PZ	21	28	22	33	0.67	15
KM	23	28	21	37	0.57	20
JB	19	35	28	43	0.65	17
RM	25	32	26	42	0.62	18
FD	25	28	25	35	0.71	22
DR	21	24	18	33	0.56	18
SV	23	32	22	38	0.58	20
GM	23	30	20	40	0.50	22
EM	23	28	20	35	0.57	20
KN	23	25	18	33	0.56	20
SM	25	28	22	36	0.61	18
BL	23	28	20	35	0.57	20
FW	23	30	22	35	0.62	20
Mean	. . .	29	22	36	0.61	19
± SD		±3	±3	±5	±0.07	±2
Range	. . .	24–35	18–28	23–43	0.5–0.78	15–22

* Manufacturer's product designation.
SD = standard deviation.

Results

In vitro study: M-mode study revealed 2 parallel echoes 2 to 3 mm wide from the anterior and posterior stents. The measured ultrasonic internal stent diameter of 20 mm was identical to the manufacturer's standard for the number 23 Ionescu-Shiley valve. The band of echoes between those from the stents corresponds with the closed cusps. M-mode measurements after suturing the valve to the nylon conduit showed an increment in width of the stent echoes to a total of 5 to 6 mm. The ultrasonic external stent diameter was 30 mm, thereby resulting in an internal to external diameter ratio of 0.67. Figure 2 shows the valve motion during 4 simulated cycles. The opening diameter of the leading edge echoes of the stent was 2.5 cm. The opening slope of the anterior cusp was 320 mm/s and the closing slope 280 mm/s. The ultrasonic cusp excursion was 18 mm compared with the manufacturer's orifice diameter of 19 mm. Echoes from the cusps in the open position had a width of 1 mm and exhibited dense high-frequency fluttering, contrasting with the linear horizontal echoes from the stent. The third cusp was not visualized, with the ultrasonic beam approaching the prosthesis from the inflow area of the valve at a 30° to 40° tilt to the sagittal and transverse planes. This orientation of the transducer produced optimal echoes and was used to obtain 2-D images, with the stents in positions 10-2-6 o'clock. Identification of the suture ring and the 3 cusps was possible by means of the short-axis plane. The long-axis sector scan disclosed echoes from 2 stents, the ring, and 2 cusps. The opening and closing motion of the Ionescu-Shiley valve cusps was consistently recorded. The cusp echo was 2 mm in width, regular, and smooth. The

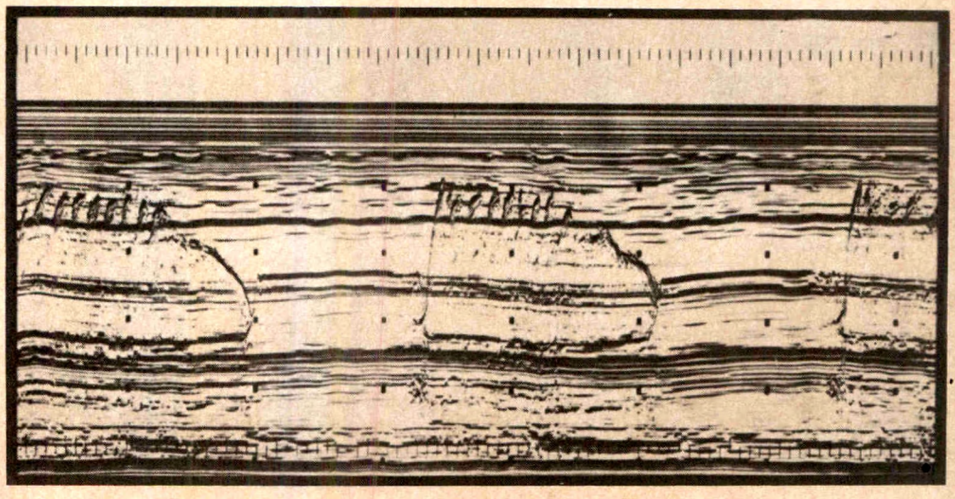

FIGURE 3. In vitro M-mode echocardiogram of the Ionescu-Shiley prosthesis after partial detachment of 1 of the cusps. Note coarse fluttering during opening of the cusps.

TABLE II M-Mode Measurements for the Ionescu-Shiley Prosthesis in the Aortic Position: Comparison With Manufacturer's Essential Dimensions

Patients	Valve Size*	Internal Diameter of Stents (mm)	Manufacturer Bare Stent Inside Diameter† (mm)	External Diameter of Stents (mm)	Manufacturer Anulus Diameter† (mm)	Cusp Excursion (mm)	Manufacturer Valve Orifice Diameter† (mm)
DP	23	18	20	23	23	. . .	19
PZ	21	22	18	33	21	15	17
KM	23	21	20	37	23	20	19
JB	19	28	16	43	19	17	15
RM	25	26	22	42	25	18	21
FD	25	25	22	35	25	22	21
DR	21	18	18	33	21	18	17
SW	23	22	20	38	23	20	19
GM	23	20	20	40	23	22	19
EM	23	20	20	35	25	20	19
KN	23	18	20	33	23	20	19
SM	25	22	22	36	25	18	21
BL	23	20	20	35	23	20	19
FW	23	22	20	35	23	20	19
Mean	. . .	22	20	36	23	19	19
± SD		±3	±2	±5	±2	±2	±2
Range	. . .	18–28	16–22	23–43	19–25	15–22	17–21

* Manufacturer's product designation.
† Manufacturer's essential dimensions.
SD = standard deviation.

long-axis view showed the central position of the closed cusps behind the stents.

M-mode echocardiograms obtained after producing a 5 mm linear tear at the base of the anterior cusp without detachment disclosed intermittent coarse fluttering below the anterior cusp in the open position. Additionally, the closing slope of the anterior cusp was reduced. Detachment of the anterior cusp from a supporting stent and ring attachment to 50% of its extension produced high-amplitude, low-frequency fluttering during ejection (Fig. 3). Alteration of the transducer position eliminated this abnormal echo, thus producing an ultrasonic configuration resembling that of the intact valve.

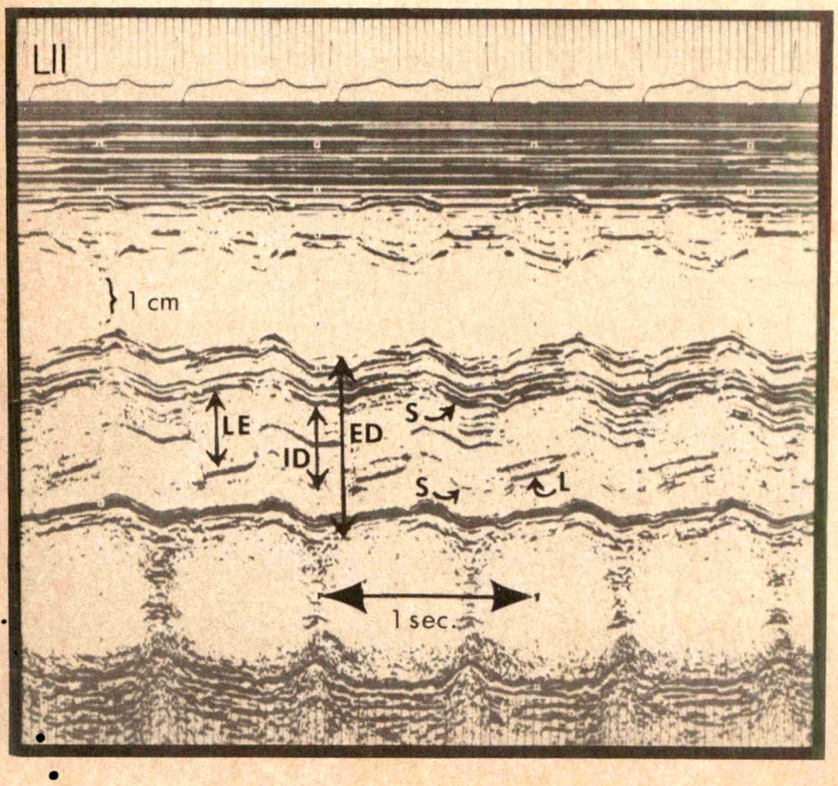

FIGURE 4. In vivo M-mode echocardiogram of the Ionescu-Shiley prosthesis in the aortic position. ED = external stent diameter; ID = internal stent diameter; L = cusp echoes; LE = cusp excursion; LII = lead II of the electrocardiogram; S = stent echoes.

In vivo study: Adequate M-mode echocardiograms were obtained in 13 of 14 patients with the prosthesis in the aortic position and in 9 of 11 patients with the valve in the mitral position. Four of 5 patients with the mitral prosthesis and 5 of 6 patients with the valve in the aortic position had satisfactory results on 2-D examination. Multiple acoustic windows, selective optimization of the settings for the prosthetic cusps, long- and short-axis and hemiaxial views were used.

M-mode values for the aortic prosthesis measurements are presented in Table I and can be summarized as follows: mean (±1 standard deviation) diameter of the leading edge of the stent = 29 ± 3 mm; internal diameter of the stent = 22 ± 3 mm; external diameter of the stent = 36 ± 5 mm; internal/external stent diameter ratio = 0.61 ± 0.07; and cusp excursion = 19 ± 2 mm.

Table II summarizes the comparison between ultrasonic measurements and the manufacturer's bare stent internal diameter, cusp excursion, and diameter of the valve orifice. The internal diameter of the stents was identical to the manufacturer's bare stent inside diameter in 6 of 14 patients (42%), and in 50% of cases the measured value was larger, mean excess being 4 mm (range 1 to 12). In only 1 patient was the measurement 2 mm less than the manufacturer's value. The measured cusp excursion compared with the manufacturer's valve orifice diameter was as follows: in 10 of 13 patients (77%) the mean excess was 1.3 mm (range 1 to 3) and in 23% this value was 3 mm (range 2 to 3) smaller than the actual diameter of the valve orifice. The measured cusp excursion was identical to the manufacturer's bare stent inside diameter in 9 of 13 patients (69%) and smaller in 3 of the 13 patients by a mean of 4 mm. In 1 patient the cusp excursion exceeded the manufacturer's value by 1 mm.

Cusp echoes were superimposed on stent echoes in 21% of patients and a third cusp echo was detected in 29% of subjects. In all patients, random punctiform "snowy" echoes were found especially with the cusps open. The opening motion of the cusps produced very rapid, faint discontinuous linear echoes. The cusp echoes during systole had a width of 1 mm and exhibited a characteristically high-frequency fluttering motion (Fig. 4).

A typical M-mode echocardiogram of a mitral Ionescu prosthesis is shown in Figure 5. M-mode measurements of the mitral prosthesis are presented in Table III and can be summarized as follows: mean diameter of the leading edge of the stent = 26 ± 3 mm; mean internal stent diameter = 23 ± 2 mm; mean external stent diameter = 32 ± 4 mm; internal/external diameter ratio = 0.758 ± 0.08; mean leaflet excursion = 21 ± 2 mm; mean initial diastolic slope of the anterior cusp = 24 ± 8 mm; mean initial diastolic slope of the stent = 23 ± 8 mm.

Comparison of the ultrasonic internal diameter of the stent with the manufacturer's bare stent inside diameter indicated that in 44% of patients, the former manifested a mean excess of 3 mm (range 1 to 6); in 33% the value was 3 mm smaller; and in 22% the measurements were identical. The measured cusp excursion was found to be 1 to 7 mm (mean 3) smaller than the manufacturer's

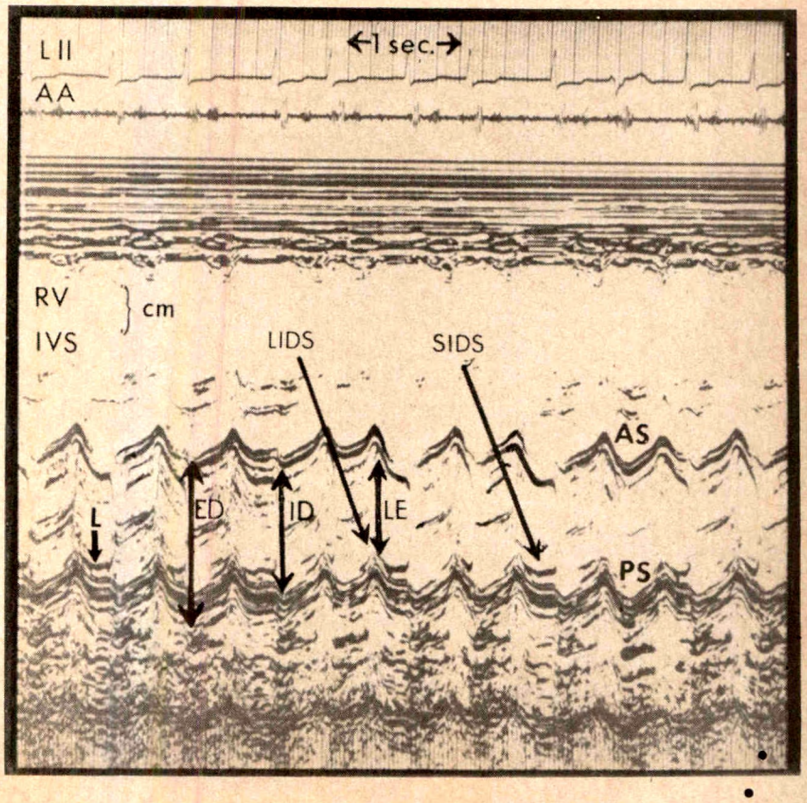

FIGURE 5. M-mode echocardiogram of the Ionescu-Shiley prosthesis in the mitral position. AA = aortic area phonocardiogram; AS = anterior stent; ED = external stent diameter; ID = internal stent diameter; IVS = interventricular septum; L = cusp echoes; LE = cusp excursion; LII = lead II of electrocardiogram; LIDS = initial diastolic slope of cusp; PS = posterior stent; RV = right ventricle; SIDS = initial diastolic slope of stent.

TABLE III M-Mode Measurements of the Ionescu-Shiley Prosthesis in the Mitral Position

Patients	Valve Size*	Diameter of Leading Edges (mm)	Internal Diameter of Stents (mm)	External Diameter of Stents (mm)	Internal/ External Diameter Ratio	Cusp Excursion (mm)	Initial Diastolic Slope of Anterior Cusp (mm/s)	Initial Diastolic Slope of Stent (mm/s)	Systolic Excursion of Anterior Stent (mm)	Left Ventricular Outflow Tract	
										End-Diastole (mm)	End-Systole (mm)
RB	25	26	24	26	0.92	22	13	13	4	10	6
DP	21	26	24	32	0.75	25	20	18	4	8	8
AC	29	30	26	40	0.65	23	43	43	7	7	1
MH	27	27	25	32	0.78	22	24	23	4	10	8
DK	29	30	23	35	0.66	23	23	20	2	15	15
IW	27	23	20	28	0.71	18	26	26	4	7	4
EV	29	20	22	30	0.73	18	20	24	6	12	9
JS	27	26	24	32	0.75	22	24	24	4	1	8
MK	25	25	23	30	0.77	20	23	20	5	8	6
JD	Suboptimal		...	...	...	...	...	...	...	...	...
CP	Suboptimal		...	...	...	...	...	...	...	...	...
Mean ± SD	...	26 ±3	23 ±2	32 ±4	0.75 ±0.08	21 ±2	24 ±8	23 ±8	4 ±1	9.6 ±4	8.2 ±4
Range	21–29	20–30	20–26	26–40	0.65–0.92	18–25	13–43	13–43	2–7	7–15	4–15

* Manufacturer's product designation.
SD = standard deviation.

TABLE IV M-Mode Measurements of the Ionescu-Shiley Prosthesis in the Mitral Position: Comparison With Manufacturer's Essential Dimensions

Patients	Valve Size*	Internal Diameter of Stents (mm)	Manufacturer Bare Stent Inside Diameter† (mm)	External Diameter of Stents (mm)	Manufacturer Anulus Diameter† (mm)	Cusp Excursion (mm)	Manufacturer Valve Orifice Diameter† (mm)
RB	25	24	22	26	25	22	21
DP	21	24	18	32	21	25	17
AC	29	26	26	40	29	23	25
MH	27	25	24	32	27	22	23
DK	29	23	26	35	29	23	25
IW	27	20	24	28	27	18	23
EV	29	22	26	30	29	18	25
JS	27	24	24	32	27	22	23
MK	25	23	22	30	25	20	21
Mean ±SD	...	23 ±2	24 ±3	32 ±4	27 ±3	21 ±2	23 ±3
Range	...	20–26	18–26	26–40	21–29	18–25	17–25

* Manufacturer's product designation.
† Manufacturer's essential dimensions.

value for orifice diameter in 78% of patients, and in 22% cusp excursion was larger by 1 to 8 mm (mean 4). In 78% of patients, the cusp excursion was 2 to 4 mm (mean 3) smaller than the measured internal stent diameter, whereas in 11% both values were identical. In the remaining 11% of subjects, cusp excursion was 1 mm larger than the internal diameter of the stents (Table IV).

The stents displayed anterior systolic motion and the mean systolic excursion of the anterior stent was 4 mm. Interventricular septal motion was paradoxical in 8 patients, flattened in 7, and normal in 4. The mean left ventricular outflow tract estimation in end-systole was 82 mm and in end-diastole 96 mm. In 6 patients, a third stent echo was observed with varying degrees of eccentricity. The closing cusp position tended to be midway between the anterior and posterior stents. In 2 patients with atrial fibrillation and R-R intervals >1,200 ms, incomplete mid-diastolic closure of anterior and posterior cusps was recorded. "Snowy" echoes were generally present. During diastole, high-frequency fluttering of the anterior and posterior cusps was present.

Identification of the posterior edge echoes of the posterior stent was generally difficult because of reverberations. Two-dimensional echocardiograms of the prosthesis in the aortic position (Fig. 6) showed minimal motion of the longitudinal axis of the stents. Cusp echoes were smooth and had a regular consistent motion in both the short and the longitudinal axis. The cusp thickness was 2 to 3 mm and the mean stent diameter 20 mm. Heavier echoes were observed at the junction of the interventricular septum with the aortic wall. Two-dimensional echocardiograms of the prosthesis in the mitral position showed similar characteristics of the

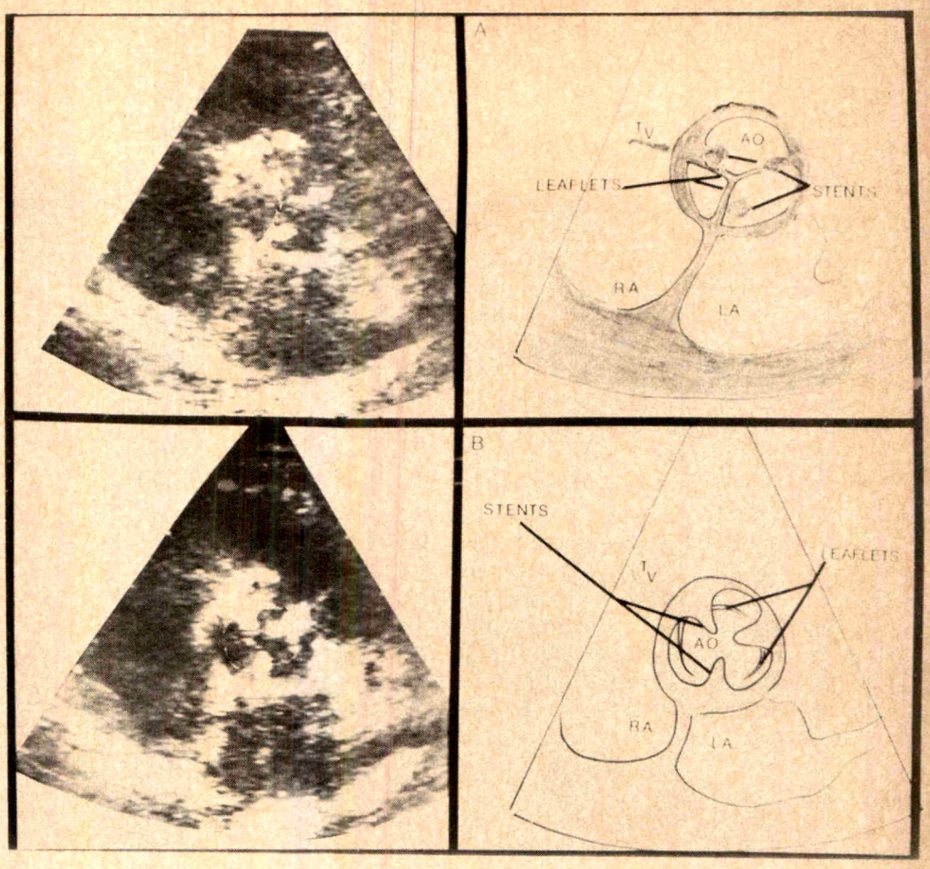

FIGURE 6. Short-axis 2-D echocardiograms of the Ionescu-Shiley prosthesis in the aortic position. **A,** valve in closed position; **B,** valve in open position. AO = aortic valve; LA = left atrium; RA = right atrium; TV = tricuspid valve.

stents, cusp motion, and thickness (Fig. 7). Heavy echoes were consistently recorded behind the posterior stent. The stent motion was concordant with motion of the ventricular posterior wall and anulus. No tilting or rocking motion was observed. Hemiaxial sector scans were also helpful in demonstrating the character of the stent echoes and cusp motion.

Discussion

This study indicates that with few exceptions, there is a reasonable approximation of manufacturer's essential dimensions and echocardiographically obtained values in subjects with the Ionescu-Shiley prosthesis.

The in vitro detachment of part of 1 cusp produced coarse fluttering of the abnormal cusp, whereas a tear in the base of 1 cusp produced occasional abnormal fluttering echoes below the affected cusp during ejection. Two-dimensional and M-mode echoes were helpful in demonstrating this abnormality. These findings agree with data of Alam et al[13] in patients with clinical porcine xenograft insufficiency. Our in vitro findings indicate that massive cusp detachment can be missed in the casual M-mode examination of this prosthesis because apparently normal echoes can be produced by changing acoustic windows and transducer angle. In such a setting, 2-D scanning of the valve disclosed the mechanical derangement. Multiaxial 2-D echocardiographic ex-

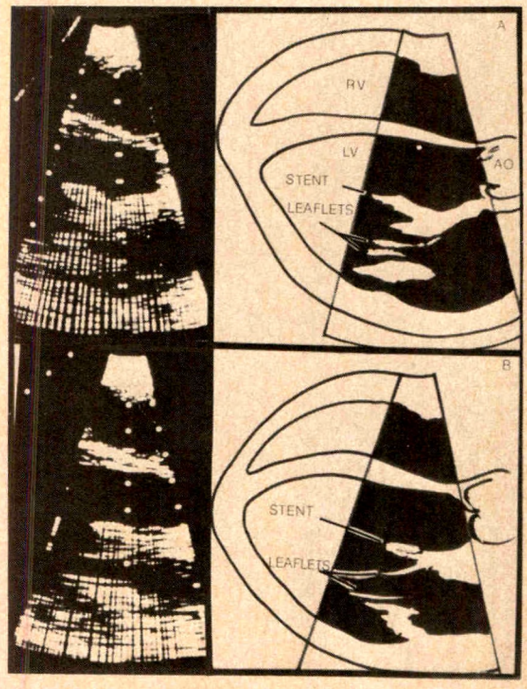

FIGURE 7. Long-axis 2-D echocardiograms of the Ionescu-Shiley mitral prosthesis. **A,** valve in closed position; **B,** valve in open position. Ao = aortic root; LV = left ventricle; RV = right ventricle.

amination of the valve using several acoustic windows is essential to evaluate the Ionescu-Shiley prosthesis. This finding accords with previous reports by Alam et al,[13] Schapira et al,[14] and Martin et al[17] regarding the superiority of 2-D sector scanning over M-mode echocardiography in the evaluation of porcine xenografts. The M-mode internal/external stent diameter has been suggested to be an index of thrombosis of the valve orifice[9] in the porcine bioprosthesis; however, technical difficulty in determining internal diameter and variations in the measurements of the external diameter[12] appear to reduce the sensitivity of these indexes. In the Ionescu-Shiley valve, we have noted variation between the measured M-mode values and the manufacturer's standard measurements. Despite these discrepancies, extreme changes in these values during the longitudinal follow-up of the individual patient will likely prove of diagnostic value. As is true for porcine xenografts, determination of external stent diameter is difficult because of reverberations behind the posterior stent, especially with the valve in the mitral position.

Two-dimensional echocardiographic determinations of cusp thickness and stent smoothness along with motion throughout the cardiac cycle are possible with the Ionescu-Shiley prosthesis in both the aortic and the mitral positions. To fully assess this prosthesis several acoustic windows in addition to the standard recording site must be employed.

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Aortic Valve Systolic Flutter as a Screening Test For Severe Aortic Stenosis

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Previous efforts using M-mode echocardiography or 2-dimensional (2-D) echocardiography have not consistently separated patients with and without significant aortic stenosis (AS). We postulated that an aortic valve sufficiently pliant to produce systolic flutter on M-mode echocardiography could exclude significant AS and reviewed the M-mode echocardiograms of 50 consecutive patients (mean age 59 years) catheterized for presumed AS; 2-D echocardiography was also performed in 18 of 50 patients (36%). In 40 of 50 patients (80%) the aortic valve cusps were easily identified on M-mode echocardiography: 19 of 40 (48%) had systolic flutter with a mean aortic valve gradient of 4 ± 8 mm Hg (mean ± standard deviation [SD]) and an aortic valve area of 2.8 ± 0.4 cm^2; 21 of 40 (52%) had no systolic flutter with a mean aortic valve gradient of 55 ± 19 mm Hg and an aortic valve area of 0.7 ± 0.3 cm^2. In the 10 of 50 patients (20%) in whom aortic valve cusps were not clearly identified, the mean aortic valve gradient was 50 ± 24 mm Hg and the aortic valve area 0.8 ± 0.4 cm^2. Systolic flutter was not seen with an aortic valve gradient >30 mm Hg or an aortic valve area <1 cm^2. Aortic valve systolic opening by M-mode echocardiography or 2-D echocardiography did not accurately predict the severity of AS. Thus, aortic valve systolic flutter seen on M-mode echocardiography is strong evidence against significant AS, but the absence of systolic flutter does not allow reliable prediction of the severity of AS. The finding of systolic flutter by M-mode echocardiography may be a useful screening test in patients presumed to have AS.

M-mode echocardiographic attempts to quantitate the degree of aortic stenosis (AS) have not been consistently successful.[1–8] Direct observation of aortic valve motion on 2-dimensional (2-D) echocardiography offered more promise,[9] but quantitation of the severity of AS in the individual is inaccurate.[10] Aortic valve systolic flutter (high-frequency oscillations of 1 or both aortic valve leaflets during systole) is a frequent M-mode echocardiographic finding in normal subjects.[1,2,11] Its presence in part reflects a pliable valve leaflet. We postulated that aortic valve systolic flutter would be seen only in patients with aortic valve disease who had at least 1 aortic leaflet sufficiently pliant that it would not significantly impede transvalvular flow. This study was designed to assess (1) how frequently aortic valve systolic flutter occurs in patients being evaluated for presumptive AS, (2) whether the presence or absence of systolic flutter of the aortic valve predicts the severity of AS as assessed at cardiac catheterization, and (3) how the predictive value of systolic flutter compares with the measurement of aortic valve systolic opening on 2-D echocardiography.

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Methods

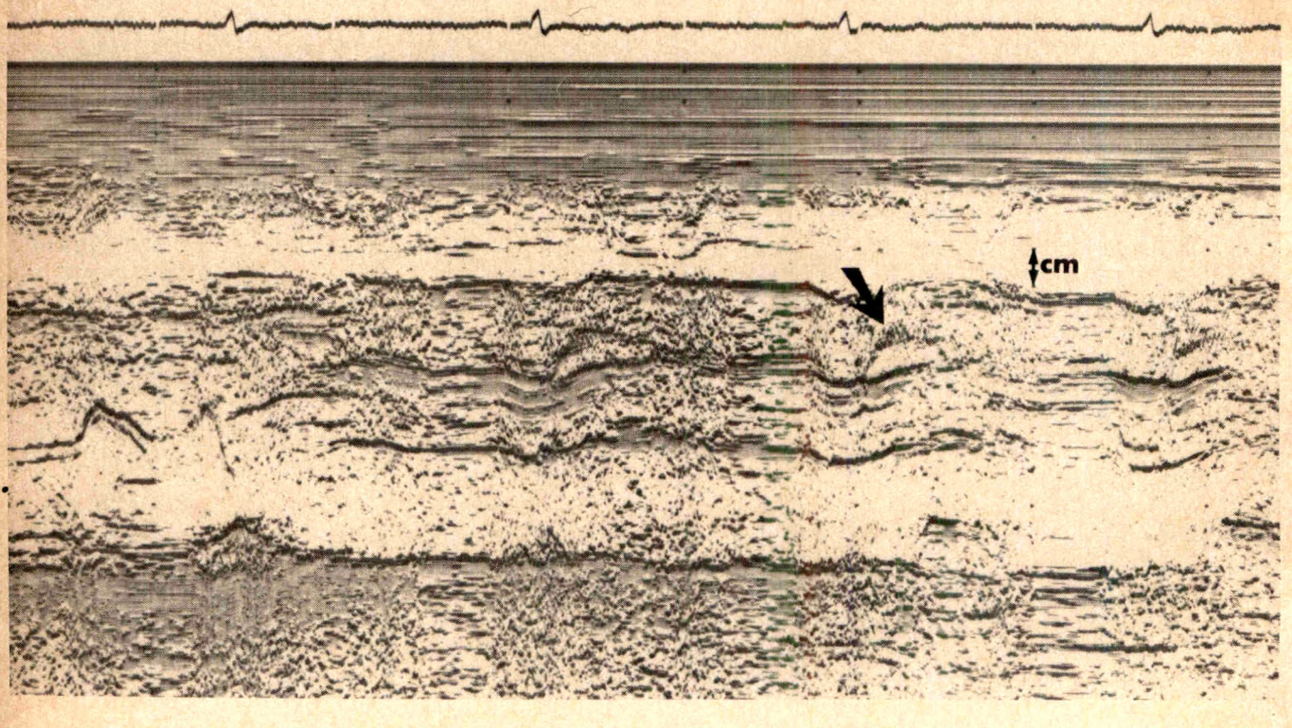
Patients: We retrospectively examined the records of all patients who underwent cardiac catheterization for evaluation of AS between January 1, 1978 and December 31, 1981 who also had M-mode echocardiography performed within 48 hours of catheterization. We excluded 4 patients, 3 because of the lack of adequate hemodynamic data and 1 because of the presence of subvalvular aortic obstruction. The resultant study group included 50 patients.

Cardiac catheterization: Right and left heart catheterization was performed in the standard manner. Aortic valve gradients were determined by simultaneous left ventricular and brachial artery pressure during retrograde left ventricular catheterization or simultaneous left ventricular and aortic pressure during transseptal catheterization. Hemodynamic data and measurements of cardiac output by the Fick method were used to derive the mean aortic valve gradient and to es-

timate the aortic valve area using the modified Gorlin formula.[12] For purposes of statistical analysis, aortic valve area was considered to be 3.0 cm^2 (normal) when the aortic valve gradient was 0,[13] because the Gorlin formula is not applicable in this situation.[12]

Echocardiography: M-mode echocardiography using a Smith-Kline Ekoline 20 recorder with a 2.25 MHz transducer and a Honeywell model 1856A fiberoptic strip chart recorder was performed using standard technique.[14] Three independent observers, with no knowledge of patient identity or the results of cardiac catheterization and 2-D echocardiography, reviewed the M-mode echocardiograms for the presence of aortic valve systolic flutter. All observers had to be in agreement for purposes of this study. Patients in whom the aortic valve leaflet could not be clearly identified were placed in the subgroup designated "Cannot Evaluate." Figure 1 shows a typical M-mode echocardiogram in an adult being evaluated for possible AS. Despite the presence of numerous dense echoes in the aortic root, at least 1 aortic leaflet can be identified and the presence of aortic valve systolic flutter is easily identified.

Two-dimensional echocardiograms were performed with an SKI Ekosector 20A system with a 30° mechanical sector scanner and a Sanyo 1/2 inch video recorder or a Toshiba SSL-53M Sonolayer V with 80° electronically phased array transducer and a Sony 1/2 inch video recorder. Standard parasternal long- and short-axis and apical 4-chamber views were obtained.[15] Two-dimensional echocardiography performed at the same time as M-mode echocardiography was available in 18 of 50 patients. In 3 of these patients, 2-D echocardiograms were technically inadequate and were excluded. The remaining 15 patients included 8 women and 7 men with a mean age of 57 years (range 22 to 78). These 2-D echocardiograms were reviewed by 3 independent observers



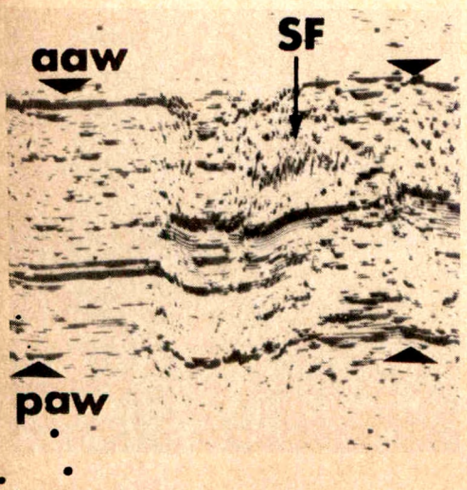


FIGURE 1. M-mode echocardiogram of aortic valve systolic flutter in a patient with no aortic valve gradient. **Top,** standard sweep from mitral valve (**left**) to aortic root. Note the heavy bands of echoes within the aortic root. Aortic valve leaflet separation is decreased (6 to 7 mm). A 1 cm calibration mark is illustrated (**double arrow**). The **large arrow** shows systolic flutter of an aortic valve leaflet. **Bottom,** enlargement of an equivalent view of the aortic valve shown in the top panel to highlight the systolic flutter (SF) of an aortic valve. aaw = anterior aortic wall; paw = posterior aortic wall.

(unaware of patient identity and the results of cardiac catherization and M-mode echocardiography) for the presence or absence of aortic valve systolic flutter in long-axis views and for maximal aortic valve leaflet separation in long- and short-axis views (Fig. 2 and 3).

Results

Complete hemodynamic records and M-mode echocardiograms were available for analysis in 50 patients. The study population was partitioned into 3 groups (Table I) according to the appearance of the aortic valve leaflets on M-mode echocardiography; the valve leaflets could not be identified by the 3 reviewers in 10 of 50 patients because of multiple linear echoes in the aortic root. These extraneous echoes are probably due to calcification or fibrosis of the aortic root wall or valve leaflets. Because the true echoes generated by the free edges of the valve leaflets could not be identified in these patients, they were grouped separately (Group I). The remaining 40 patients were divided into 21 patients (52%) without aortic valve systolic flutter (Group II) and 19 patients (48%) who demonstrated aortic valve systolic flutter (Group III). The 3 groups are summarized in Table I.

TABLE I Characteristics of Patient Population

	Group I (n = 10)	Group II (n = 21)	Group III (n = 19)
Mean age (yr)	56	61	49
Males	5	13	7
Females	5	8	12
Mitral stenosis	1	3	8
Mitral regurgitation	2	11	10
Aortic regurgitation	5	16	10
Aortic valve gradient (mm Hg)	50 ± 24	55 ± 19	4 ± 8
Aortic valve area (cm^2)	0.8 ± 0.4	0.7 ± 0.3	2.8 ± 0.4

M-mode echocardiography: The aortic valve gradient and the aortic valve area (mean ± SD) in Groups I and II were similar (Table I). Patients in Group III demonstrated a lower average aortic valve gradient and a larger aortic valve area than did patients in Groups I and II ($p < 0.001$).

Data were stratified according to those with and those without significant AS (for purposes of statistical analysis, mean aortic valve gradient was ≥30 mm Hg and calculated aortic valve area was ≤1.0 cm^2). Of 31 patients without systolic flutter (Groups I and II), 26 (84%) had an aortic valve gradient ≥30 mm Hg and 28 (90%) had an aortic valve area ≤1.0 cm^2. In Group III, only 1 patient (5%) had an aortic valve gradient equal to 30 mm Hg; none had a gradient >30 mm Hg or aortic valve area ≤1.0 cm^2 (Table II).

In the 40 patients in whom aortic leaflets could be clearly identified by M-mode echocardiography (Groups II and III), the *accuracy* ([true-positive + true-negative] ÷ [total number of tests]) of aortic valve systolic flutter in excluding hemodynamically significant AS was 95%. If aortic valve systolic flutter was present, the *predictive value* ([true-positive] ÷ [true-positive + false-negative]) of this finding in identifying patients without hemodynamically significant AS was 95%.

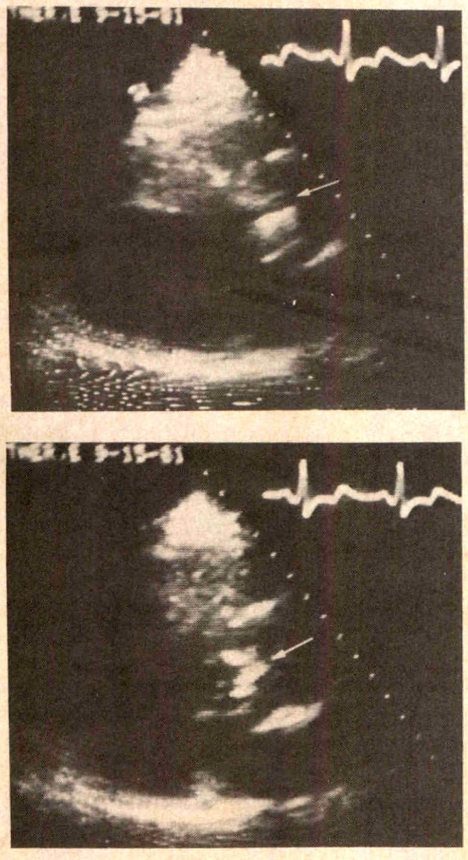


FIGURE 2. Parasternal long-axis 2-D echocardiogram of patient in Figure 1 with no aortic valve gradient. **Top,** maximal systolic opening of aortic valve (**arrow**) is 5 to 6 mm. Frame is at low gain in order to visualize leaflet separation on the heavily calcified aortic valve. **Bottom,** diastolic closure of the same heavily calcified aortic valve.

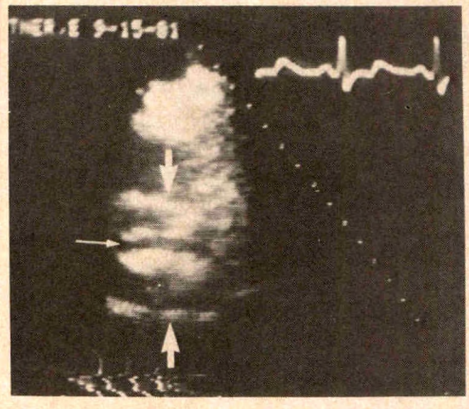


FIGURE 3. Parasternal short-axis 2-dimensional echocardiogram of the aortic valve in the patient in Figure 2. Maximal anteroposterior systolic separation (**small arrow**) of the heavily calcified aortic valve is 5 mm. **Large arrows** indicate anterior and posterior walls of the aortic root.

TABLE II Two by Two Contingency Tables Relating the Severity of Aortic Stenosis to the Presence or Absence of Aortic Valve Systolic Flutter in Group II and III Patients

	Systolic Flutter	
	+	−
Aortic valve area		
≤ 1.0 cm^2	0	19
>1.0 cm^2	19	2
	$\chi^2 = 32.74$; $p < 0.0001$	
Aortic valve gradient		
≥ 30 mm Hg	1	19
<30 mm Hg	18	2
	$\chi^2 = 28.97$; $p < 0.0001$	

Two-dimensional echocardiography: Two-dimensional echocardiograms, available for review in 18 patients, were technically adequate for evaluation of the aortic valve in 15 patients. The aortic valve area was >1.0 cm^2 in 7 patients, but aortic valve systolic flutter was noted on the 2-D echocardiogram in only 1 patient (14%). In contrast, M-mode echocardiography showed systolic flutter in 6 of these 7 patients. Aortic valve systolic opening estimated by 2-D echocardiography only generally corresponded with the aortic valve area obtained by catheterization and was not as accurate in allowing stratification of patients as was the presence of aortic valve systolic flutter on M-mode echocardiography. The aortic valve systolic opening on 2-D echocardiography measured 12 ± 5 mm (range 6 to 18) in patients with a valve area >1.0 cm^2 and was 8 ± 4 mm (range 5 to 14) in patients with a valve area ≤ 1.0 cm^2.

Discussion

Our study demonstrates that at least 1 aortic valve leaflet is identifiable on M-mode echocardiography in 80% of adults with suspected AS. Clear visualization of high-frequency systolic flutter on an aortic leaflet reliably excluded hemodynamically significant AS. No patient with aortic valve systolic flutter on M-mode echocardiography had an aortic valve area <1.0 cm^2 or an aortic valve mean gradient >30 mm Hg at cardiac catheterization.

We defined the hemodynamic severity of AS by the Gorlin formula,[12] which required a measured transvalvular gradient and forward transvalvular flow to calculate the aortic valve orifice area. For this study, we selected a gradient (mean) of ≥ 30 mm Hg and an aortic valve area ≤ 1.0 cm^2 as hemodynamic evidence of "significant" or severe AS. With aortic regurgitation, the Fick cardiac output underestimates the aortic transvalvular forward flow. Thus, *calculated* aortic valve orifice area would represent the minimum; *actual* aortic valve area may be larger. This finding does not decrease the value of the *presence* of aortic valve systolic flutter in excluding severe AS. At least 50% of patients in each group had angiographic evidence of aortic regurgitation, making it unlikely that the presence or absence of aortic regurgitation plays a predominant role in the production of aortic valve systolic flutter. Because of the sizable minority (20%) of patients in whom aortic valve leaflets were not easily identifiable, the absence of systolic flutter cannot reliably be used to diagnose significant AS. Because of the high-frequency systolic flutter, the small amplitude oscillations, and the lower sampling rate of 2-D echocardiography, it is no surprise that 2-D echocardiography (even with a high-resolution, narrow angle sector scanner) was not as sensitive as M-mode echocardiography in identifying aortic valve systolic flutter. The true systolic separation of the aortic leaflets on 2-D echocardiography was often obscured by echoes reverberating from calcification or thickening of the aortic root or valve in both the long- and short-axis parasternal views. Thus, 2-D echocardiography was of limited usefulness in stratifying patients with and without significant AS.

Clinical assessment of the severity of aortic valvular obstruction in adults with presumed AS can be difficult. Patients may have significant obstruction with few or no symptoms, and in the presence of advanced age, systemic hypertension, or left ventricular dysfunction, the physical signs of severe AS can be misleading.[16–18]

Correlation of a number of M-mode echocardiographic features of aortic valve disease such as aortic leaflet thickening, extraneous aortic root echoes, or reduced aortic valve leaflet separation, and the hemodynamic severity of AS have met with limited success.[1–5] An empiric wall stress constant derived from M-mode measurements of left ventricular dimensions and wall thickness has been useful in predicting the degree of AS in children and in some adults. Technical limitations or the presence of systemic hypertension, left ventricular dysfunction, or aortic insufficiency renders this method inapplicable in many adults.[6–8]

With superior spatial representation, 2-D echocardiographic direct measurement of aortic valve orifice areas seemed possible.[9] As in our study, further investigation has revealed the inaccuracy of this method.[10] Pulsed Doppler echocardiography, by examining blood flow characteristics in the ascending aorta, has reportedly been useful in screening patients for possible severe AS.[19] This method may not be applicable when transvalvular flow is significantly altered, as in aortic regurgitation or low cardiac output. Proper interpretation of the pulsed Doppler record in AS requires methodical examination and knowledge of the flow system beyond the stenotic valve.[20] More promising, continuous wave Doppler can be used to record the maximal velocity of the stenotic jet to estimate the pressure gradient, using the Bernoulli equation.[21]

In our laboratory, physicians frequently request an echocardiogram to evaluate the cause of a systolic murmur. The referred patients often have nonspecific findings on history and physical examination. Electrocardiographic abnormalities such as voltage criteria for left ventricular hypertrophy are frequent, but their significance is unclear because many of these patients have a history of systemic hypertension. Many patients will demonstrate increased echoes in the aortic root on M-mode echocardiography, which are not specific for aortic valvular obstruction. The echocardiographer is

obligated to interpret such tracings as being consistent with either aortic stenosis or sclerosis. By searching for aortic valve systolic flutter, a more accurate estimation of the likelihood of significant AS can be made. Simple detection of aortic valve systolic flutter makes severe AS unlikely and should be clinically useful in the decision-making process regarding the need for cardiac catheterization. Conversely, the absence of aortic valve systolic flutter does not necessarily indicate significant AS.

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Detection and Estimation of Rheumatic Mitral Regurgitation In the Presence of Mitral Stenosis by Pulsed Doppler Echocardiography

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The sensitivity and specificity of pulsed Doppler echocardiography (PDE) in diagnosis and estimation of the severity of mitral regurgitation in the presence of rheumatic mitral stenosis was studied in 34 patients (18 women and 16 men) ranging in age from 33 to 70 years (mean 55). Definitive diagnosis of mitral regurgitation was confirmed in all patients by angiography and in 20 patients also by indicator dilution technique. Mitral regurgitation was detected by PDE in all patients with angiographically proven severe mitral regurgitation and in 7 of 8 patients with moderate mitral regurgitation. In patients with trace to mild mitral regurgitation, PDE was positive in only 7 of 13 patients. When subdivided for mild, moderate and severe mitral regurgitation, PDE sensitivity for diagnosis was 54, 88, and 100%, respectively; overall accuracy was 79% and specificity was 100%.

Average systolic dispersion on time-interval histogram was 59% for mild, 89% for moderate, and 100% for severe mitral regurgitation. Groups of patients with mild mitral regurgitation could be differentiated from those with moderate ($p < 0.05$) and severe ($p < 0.01$) mitral regurgitation. A significant overlap of individual values, however, occurred. In 7 of 11 patients with moderate to severe mitral regurgitation, systolic turbulence also was detected in the left atrium. PDE was sensitive and specific in diagnosing moderate to severe mitral regurgitation in the presence of mitral stenosis. Assessment of precise severity of mitral regurgitation is still a problem in individual patients.

M-mode and 2-dimensional echocardiography are useful noninvasive techniques in the diagnosis and assessment of severity of rheumatic mitral stenosis.[1–3] These techniques, however, provide little direct information about associated mitral regurgitation. Since there is an increasing trend among cardiologists to subject patients with mitral stenosis and other valvular heart disease to cardiac surgery[4–6] based on clinical and echocardiographic evaluation without doing cardiac catheterization, additional information about associated regurgitation could be helpful in deciding preoperatively whether a patient should undergo mitral valve repair or replacement. Range-gated pulsed Doppler echocardiography (PDE) noninvasively identifies blood flow patterns at well-defined locations in the heart and detects stenotic or regurgitant lesions.[7] In this study, the sensitivity and specificity of PDE in diagnosing and estimating the severity of mitral regurgitation in the presence of mitral stenosis was examined.

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Methods

Thirty-four patients (18 women and 16 men) with mitral stenosis, ranging in age from 33 to 70 years, were studied by PDE between January 1978 and December 1981. The severity of mitral regurgitation was assessed clinically by an attending cardiologist based on characteristics of the left ventricle and systolic murmur. Most of these patients were studied by PDE within 48 hours of cardiac catheterization. PDE was performed in all patients by a technician who was unaware of clinical or angiographic diagnosis. Eighteen healthy medical students in whom organic heart disease was excluded by usual clinical means served as control subjects.

Cardiac catheterization: The severity of mitral stenosis was estimated by measuring the mean diastolic gradient across the mitral valve from simultaneously recorded pulmonary artery wedge or left atrial pressure and the left ventricular

diastolic pressure tracings, and by calculating mitral valve orifice using Gorlin's formula. Mitral stenosis was considered mild when the mitral valve orifice was 1.5 to 2.5 cm^2, moderate when it was 1.0 to 1.5 cm^2, and severe when it was <1 cm^2. Mitral regurgitation was assessed from the amount of opacification of the left atrium by contrast material after left ventriculography. It was classified as mild if there was minimal staining of the left atrium which cleared rapidly, moderate if the left atrium was opacified with slow clearing, and severe if complete opacification of the left atrium occurred with the first cycle and continued throughout the entire period of ventriculography.

Mitral regurgitation was further confirmed in 20 patients by indicator-dilution curves. A catheter (size 8 rattail) was placed in the left ventricle. The transseptal catheter was placed in the left atrium above the mitral valve. Indocyanine green dye (0.06 mg/kg) was flushed carefully with 6 ml of saline solution through the catheter in the left ventricle. Sampling from the left atrium and femoral artery was done through cuvette densitometers with constant withdrawal syringes (Harvard Apparatus, Millis, Massachusetts). A Hewlett-Packard recorder was used to record dye curves. Depending on the time of appearance, the amount of dye in the left atrium, and configuration of the dye curves, mitral regurgitation was graded as mild, moderate, or severe.[8,9]

Doppler echocardiography: Initially we studied 12 patients and 9 medical students using an ATL (Advanced Technology Laboratories, Bellevue, Washington) 500A pulsed Doppler echocardiograph with a Honeywell 1856 ultraviolet recorder. This instrument employs a single 3 MHz piezoelectric transducer, 0.5 inch in diameter and focused at 5 cm, which operates simultaneously for both Doppler and echocardiographic procedure (M-mode PDE). We studied the remaining 22 patients since August 1979 using the Mark V ATL system which provides real-time images of cardiac structures, which can be frozen to allow investigation of blood flow by 2-dimensional PDE. The frozen-section image has a superimposed radial line with a bright spot (Doppler sample volume). The operator can move the line radially across the image and adjust depth of the sampling site by moving the bright spot along the line to an appropriate position.

In both systems, flow can be detected in a teardrop-shaped region approximately 2 mm in diameter and 4 mm in length at any depth from 2 to 15 cm along the ultrasonic beam. Two types of output are available from this device. The first is an audio signal (400 Hz to 5 kHz) that corresponds to the spectrum of Doppler shifts produced by normal or disturbed blood flow and allows interpretation based on tonal quality. The second is an on-line graphical display of the Doppler shift frequencies (time-interval histogram [TIH]) which is printed on a strip-chart recorder. Laminar blood flow produces a narrowly clustered dot pattern (narrow-band pattern) because reflected sound waves have a fairly uniform Doppler shift. Turbulent flow produces a widely dispersed dot pattern (wide-band pattern) because blood cells have varied direction and velocity. Principles and use of TIH are described in detail by Lorch et al.[10]

With the patient in supine or left lateral position, the mitral valve was located and the M-mode PDE transducer was oriented so that the ultrasonic beam was almost parallel to the axis of flow to insure maximal blood flows. Mitral valve, intermediate area, anulus, and the left atrium were carefully explored for mitral stenosis and regurgitation.

In patients studied by 2-dimensional PDE, blood flow information was also obtained from similar mitral valve areas. Since 2-dimensional echocardiography has better spatial resolution than M-mode, it was possible to sample blood flow velocities in long-axis, short-axis and 4-chamber apical views.

The threshold control was adjusted to eliminate most background noise. The Doppler gain was adjusted so that the input signal presented as peaks, off the baseline. The audio signal and the frozen 2-dimensional image of the mitral valve, with superimposed line delineating position of the Doppler sample volume, were recorded on a video cassette recorder (Sanyo model VTC 7100); TIH was printed on a fiber optic

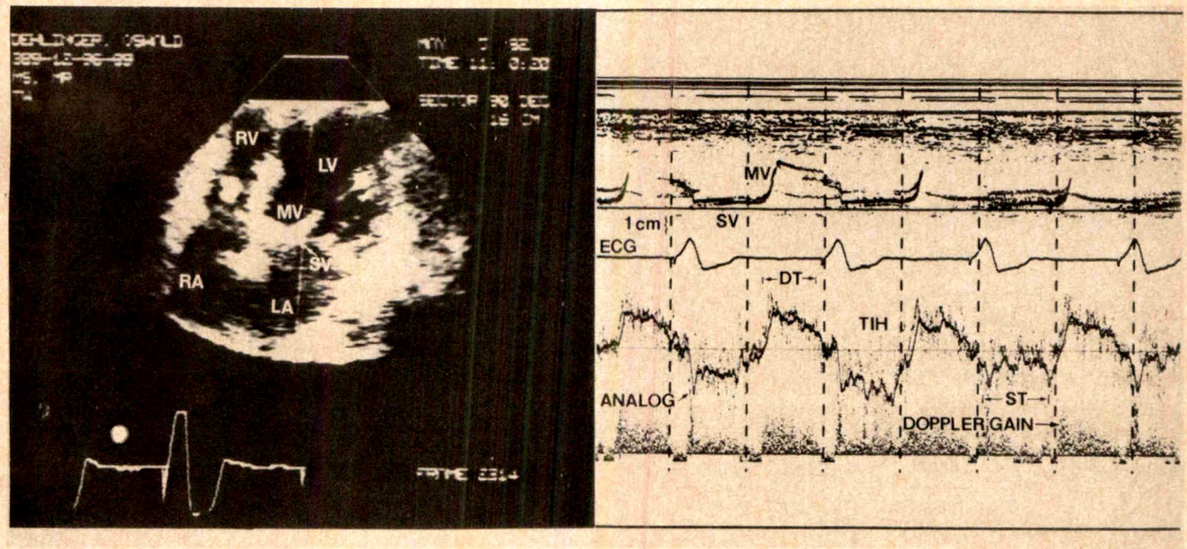

FIGURE 1. Pulsed Doppler echocardiographic examination over left ventricular inflow region from apical 4-chamber view. The **left panel** shows a continuous line with a dot indicating the position of the sample volume (SV). The **right panel** indicates the position of the SV on M-mode echocardiogram (upper half) and time-interval histogram (TIH) (lower half). Note the turbulent (wide scattering of dots) diastolic flow indicating mitral stenosis and the negative turbulent flow in systole indicating mitral regurgitation. The superimposed analog flow signal shows a serrated, uneven pattern. DT = diastolic turbulence; LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle; ST = systolic turbulence.

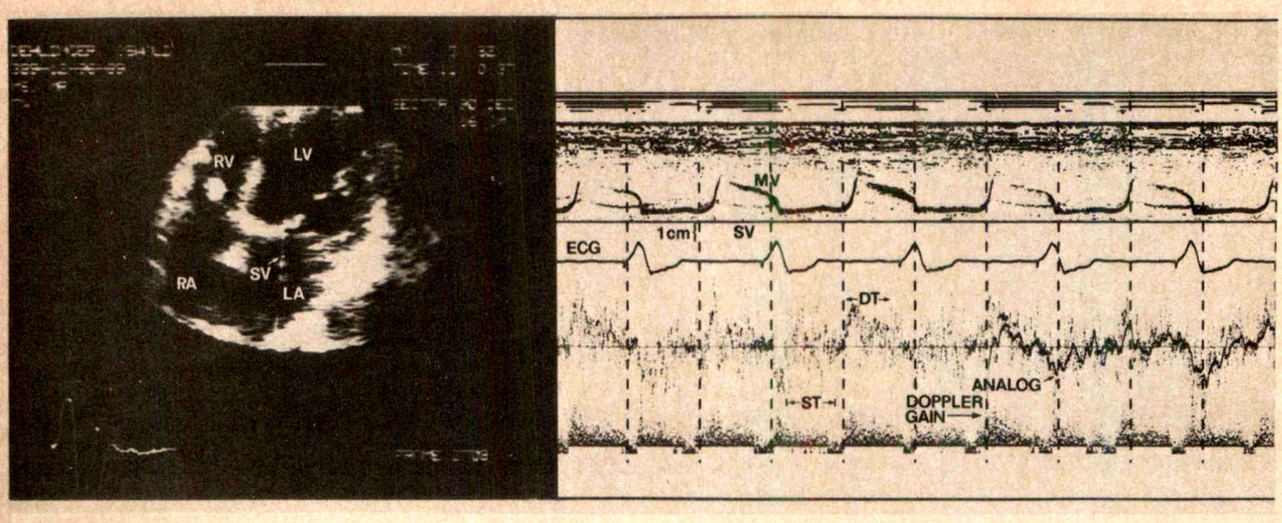

FIGURE 2. Pulsed Doppler examination of the same patient with sample volume placed deeper in the left atrium. Diastolic and systolic turbulence is again noted, although forward and reverse direction of blood flow is not as striking compared with sampling over left ventricular inflow region. Abbreviations as in Figure 1.

recorder at a paper speed of 25 to 40 mm/s. An analog flow velocity curve which represents an average of Doppler shift frequencies was also superimposed on the TIH. Detection of turbulent flow confirmed the diagnosis of mitral stenosis when present in diastole, and mitral regurgitation when in systole. The width and configuration of special dispersion on TIH from 5 consecutive cycles were analyzed in all patients. For mitral regurgitation, the ratio of maximal systolic dispersion on TIH to total duration of systole was calculated (Fig. 1). The systolic dispersion on TIH was divided into 3 segments corresponding to mild (<50%), moderate (50 to 75%), and severe (>75%) turbulence. A relation between amplitude, width, and breadth of negative wave on analogue and severity of mitral regurgitation has been noted by Kalmanson et al.[11] Severity of mitral regurgitation was also assessed by tracing the systolic turbulence from mitral leaflets to the left atrium (Fig. 2).[12,13]

Results

Cardiac catheterization data: The average diastolic gradient and calculated mitral valve orifice size in 33 patients is summarized in Table I. A majority of the patients had moderate to severe mitral stenosis. In 2 patients with predominant mitral regurgitation, only an early diastolic gradient was noted. In 1 patient with severe mitral stenosis and a large left atrial thrombus partially blocking the pulmonary veins, pulmonary artery wedge pressure could not be obtained.

Correlation was good between the clinical diagnosis of the presence of mitral regurgitation and diagnosis by the angiographic or dye-dilution method, as illustrated by Figure 3. However, 4 false-positive diagnoses were

TABLE I Distribution of 33 Patients With Mitral Stenosis According to Average Mitral Valve Orifice Size and Diastolic Pressure Gradient

Mitral Stenosis	Mild	Moderate	Severe
Mitral valve orifice (cm^2)	>1.5	1.0–1.5	<1.0
Diastolic pressure gradient (mm Hg)	<10	10–20	>20
Average mitral valve orifice size	2.64 (8)*	1.25 (11)	0.76 (14)
Average diastolic pressure gradient	6.7 (8)	15.4 (17)	26.8 (8)

* Number in parentheses indicates number of patients.

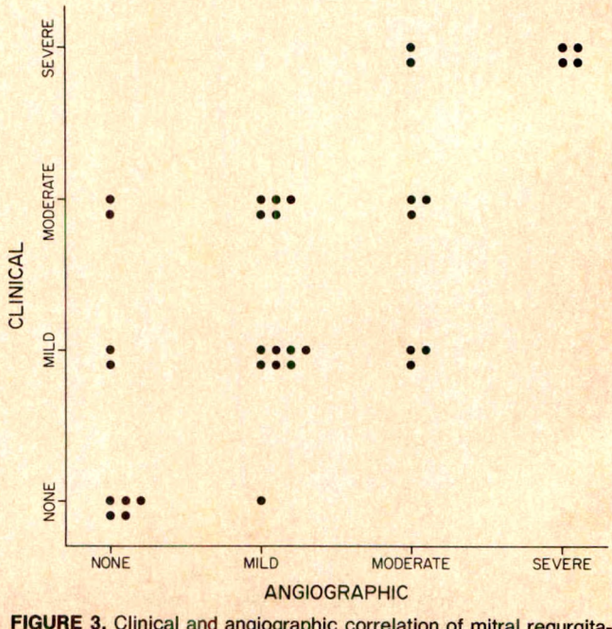

FIGURE 3. Clinical and angiographic correlation of mitral regurgitation.

TABLE II Angiographic and Doppler Correlation of Mitral Regurgitation

Mitral Regurgitation	Angiography	Doppler				
		Negative	Positive	% TIH		
None	9	9	0	0		
Mild	13	6	7	59	$p < 0.05$	$p < 0.01$
Moderate	8	1	7	88		
Severe	4	0	4	100	$p > 0.02$	
Total	34	16	18			

TIH = average percent systolic turbulence.

made clinically, while none was documented during cardiac catheterization. There was also considerable disparity between clinical and angiographic assessments of the severity of mitral regurgitation. While severe cases of mitral regurgitation correlated well by both methods, there was significant disparity in mild and moderate cases. A significant disparity was also noted between clinical and PDE assessment of presence and severity of mitral regurgitation (Fig. 4).

Doppler data: *Normal subjects:* The spectral pattern for diastolic flow across the normal mitral valve mimicked the motion of the anterior leaflet echogram of the mitral valve. Nonturbulent, anteriorly directed flow was found to commence with the opening of the mitral valve in all patients. This flow diminished until late diastole, when a second peak occurred with atrial contraction. The early and late diastolic flows were separated in mid-diastole by what appeared to be a period of virtually no detectable flow or by an intermediary peak. During isometric contraction of the left ventricle, a brief negative deflection was seen in most subjects. Systolic turbulence, by audio signal or TIH, was not detected in any of the normal subjects.

Mitral stenosis: Abnormal diastolic turbulence was noted in all except 2 patients—1 with severe and the other with mild mitral stenosis. Overall sensitivity in diagnosis of mitral stenosis was 94%. There was no correlation between severity of mitral stenosis and type of blood flow patterns obtained on TIH.

Mitral regurgitation: Pulsed Doppler echocardiography did not detect any mitral regurgitation in the control group of 18 healthy medical students or in 9 patients with pure mitral stenosis without mitral regurgitation on ventriculography or dye-dilution curves. Therefore, overall specificity was 100%.

Mitral regurgitation was detected by PDE in all patients with angiographically proven severe mitral regurgitation and in 7 of 8 patients with moderate mitral regurgitation. In patients with trace to mild mitral regurgitation, however, PDE was positive in only 7 of 13 patients (Table II). Overall sensitivity in detecting mitral regurgitation for all patients was 72%. When subdivided for mild, moderate, and severe mitral regurgitation, PDE sensitivity for diagnosis was 54, 88, and 100%, respectively. Overall accuracy was 79% and specificity was 100%.

Average systolic dispersion on TIH was 59% for mild, 88% for moderate, and 100% for severe mitral regurgitation. Groups of patients with mild mitral regurgitation could be distinguished from those with moderate ($p < 0.05$) and severe ($p < 0.01$) mitral regurgitation; however, there was considerable individual overlap and the latter 2 groups could not be separated based on TIH alone.

Severity of mitral regurgitation was also assessed by tracing systolic turbulence from mitral valve to the left atrium. In 7 out of 11 patients with moderate to severe mitral regurgitation systolic turbulence was detected in the left atrium. Only 1 patient with mild mitral regurgitation had detectable systolic turbulence in the left atrium.

PDE was therefore both sensitive and specific in diagnosing moderate to severe mitral regurgitation in the presence of mitral stenosis. Overall correlation between PDE and angiography in the diagnosis of trace to mild mitral regurgitation was poor. Assessment of severity of mitral regurgitation by time-interval histogram, in individual patients, is still a problem.

Discussion

Evaluation of mitral regurgitation is difficult by any presently accepted method; therefore, any new method must be examined carefully. Traditionally, the surgeon evaluated mitral regurgitation at operation by palpating the regurgitation jet which came through the valve into

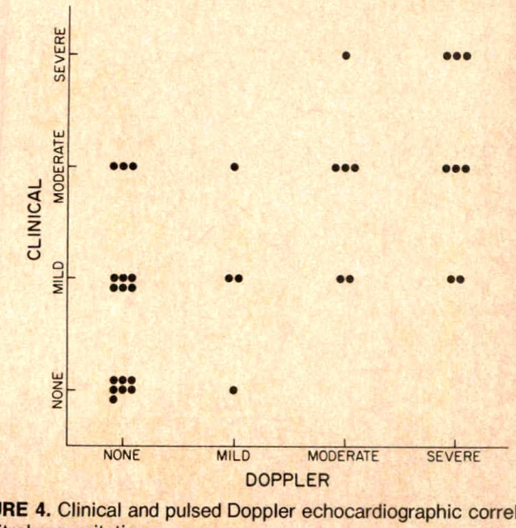

FIGURE 4. Clinical and pulsed Doppler echocardiographic correlation of mitral regurgitation.

the left atrium during systole. Unfortunately, this method is not reliable because it depends on the force of left ventricular contraction, systolic and left atrial blood pressure, and the size of the regurgitant orifice. This technique is still used and is usually part of the clinical decision concerning valve replacement. The catheterization technique, which depended on the contour of the left atrial pressure and the height of the V wave, quickly fell into disrepute because of significant discrepancies.[14] The angiographic method also has known errors created by premature contractions, arrhythmias, diastolic regurgitation, distortion of valve closure by the catheter, and the problems created by inadequate mixing of blood and contrast material in the ventricle. If a small amount of regurgitated blood contains a high concentration of contrast material, regurgitation will appear to be greater than if little or no contrast material enters the atrium with regurgitated blood. Hence estimations of insufficiency are highly dependent on the position of the cardiac catheter, as well as the rate and timing of contrast injection. However, this method is the most widely employed means of assesing mitral regurgitation. Mitral regurgitation can also be quantified by comparing angiographic left ventricular stroke volume and the effective or forward stroke volume by Fick or indicator-dilution methods.[15] M-mode echocardiography, a noninvasive technique, is useful in diagnosing the cause of mitral regurgitation, but the hemodynamic abnormality is assessed by secondary and nonspecific features such as the size of the left atrium, the pulsations of the left atrial wall, the size of the left ventricle, and the pattern of interventricular septal motion.[16,17] In rheumatic mitral valve disease, echocardiographic features of mitral stenosis are dominant and mitral regurgitation may not be detected. Occasionally, in predominant rheumatic mitral regurgitation there is so-called ski sloping with an initial brisk downward E to F slope of anterior mitral leaflet with a subsequent flatter slope during the later portion of diastole.[18] This echocardiographic sign is occasionally useful but not totally reliable. On the 2-dimensional echocardiogram left atrial volume overload may be seen in severe mitral regurgitation.[19] The regurgitant mitral orifice may be recorded in patients with rheumatic mitral regurgitation.[20] However, this observation has not been confirmed by other investigators. Therefore, there is considerable interest in the recently introduced PDE technique which delineates blood flow patterns at well-defined cardiac locations.

Since Johnson et al[21] originally reported detection of mitral regurgitation by PDE, a number of reports have appeared confirming reliability of the technique.[11–13,22] Abbasi et al[12] found a specificity of 96% and a sensitivity of 92% in detection of mitral regurgitation. Of 23 patients with mitral regurgitation, 8 had rheumatic mitral disease and all were diagnosed by PDE. Abbasi et al also found a high correlation between severity of mitral regurgitation assessed by contrast ventriculography compared with PDE ($r = 0.88$; $p < 0.01$ by Pearson method). Our study also shows that PDE is sensitive in diagnosis of moderate and severe mitral regurgitation associated with varying degrees of mitral stenosis. There was only 1 false-negative result in the group with moderate mitral regurgitation. This patient had severe mitral stenosis and aortic regurgitation with a low cardiac output (cardiac index 1.241 liters/m^2). Therefore, turbulence created by mitral regurgitation may not have been severe enough to be detected by PDE. The sensitivity of PDE in diagnosis of mild mitral regurgitation was low, with only 7 out of 13 cases diagnosed. Because the sample volume is small, fixed, and single, it is possible to miss a localized jet of regurgitation in spite of careful exploration. The sensitivity of the PDE in the diagnosis of mild mitral regurgitation might have been higher if the examination had been done with the knowledge of the presence of mild mitral regurgitation on clinical evaluation and a systolic turbulence searched for more judiciously. The results of our PDE study indicate an excellent correlation in detection of moderate and severe mitral regurgitation associated with mitral stenosis. Although the degree of systolic turbulence on TIH and radiation to left atrium provides reasonably objective criteria for assessment of severity of mitral regurgitation, a significant overlap of individual values between groups is a limiting factor in the use of this technique to quantify the degree of mitral regurgitation.

Limitations of the study: Although the PDE diagnosis of mitral regurgitation was based on interpretation of TIH, the technical skill of the operator remains an important factor in obtaining an accurate study. TIH is dependent on threshold and Doppler gain settings which have to be constantly adjusted; otherwise, electronic "noise" inherent in the instrument may cause wide-dot or turbulent pattern even when blood flow is normal. The operator must be able to decipher the audio signal, explore blood flows from mitral valve at different angles to detect maximal flows, and trace the regurgitant jet to the left atrium to define an area of distribution of turbulent flow.

Because the PDE system used in our study has a single gate and a fixed sample volume, a localized jet of turbulent flow may be missed, as was evident in 6 of 13 patients with mild mitral regurgitation. It is also difficult to map the area of turbulent flow precisely. A newer instrument with a multigated system[23] and the ability to change Doppler sample volume[24] and color-coded Doppler visualization of flow[25,26] may substantially improve overall sensitivity in diagnosing and assessing severity of lesions.

Since TIH is a zero-crossing detector and does not accurately reflect the true Doppler shift frequencies, precise quantification of blood flow velocities or volume flow is not possible. To quantify volume flow, one must know true Doppler shift, valve orifice size, and the angle at which Doppler shift is obtained. With 2-dimensional echocardiography, it is possible to obtain valve orifice size and, with newer digital technology, true Doppler shift frequencies. Precise delineation of sampling angle remains a problem.

Clinical implications: Mitral regurgitation is frequently associated with mitral stenosis because of loss of valve substance, rigidity of leaflets, and shortening of chordae tendinae, all of which do not allow the mitral

valve to coapt properly in systole. Depending upon the degree of distortion of valvular and subvalvular structures, hemodynamic abnormality of mitral regurgitation varies and is of clinical importance in moderate and severe cases. Combined mitral stenosis and mitral regurgitation produce symptoms early, result in more severe pulmonary hypertension because of both pressure and volume overload, and have greater susceptibility to both bacterial endocarditis and left ventricular dysfunction. Therefore it is beneficial to assess correctly each possible lesion by combined 2-dimensional PDE.

Surgical management of patients with predominant mitral stenosis differs from that of patients with mitral regurgitation. In pure mitral stenosis, with pliable leaflets, commissurotomy is the treatment of choice, whereas with associated moderate or severe mitral regurgitation the valve needs to be replaced. There is an increasing tendency to subject patients with mitral stenosis to surgery based on echocardiographic findings without prior cardiac catheterization. Since information regarding mitral regurgitation is indirect and often not present on M-mode or 2-dimensional echocardiography, Doppler information could be helpful in deciding preoperatively whether a patient should undergo commissurotomy or mitral valve replacement.

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Clinical and Echocardiographic Characteristics of Patients With Mitral Anular Calcification

Comparison With Age- and Sex-Matched Control Subjects

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The clinical and echocardiographic features of 104 patients (53 women and 51 men) with mitral anular calcification (MAC) were compared with those of 121 age- and sex-matched control subjects (62 women and 59 men) without MAC. The incidence of coronary artery disease, rheumatic heart disease, systemic hypertension, and diabetes mellitus was similar in both groups. Patients with MAC had a greater incidence of cardiomegaly ($p < 0.001$), cardiac conduction defects ($p < 0.001$), and aortic outflow tract murmurs ($p < 0.005$) than did control patients. Patients with MAC and without aortic root calcification had a higher incidence ($p < 0.001$) of conduction defects than did patients with aortic root calcification without MAC. Control patients with and without aortic root calcification had a similar incidence of conduction defects. A higher incidence of atrioventricular block ($p < 0.025$) and bundle branch block or left anterior hemiblock or intraventricular conduction defect ($p < 0.05$) was present in anterior MAC than in posterior MAC. In conclusion, patients with MAC have a higher incidence of cardiomegaly, cardiac conduction defects, and aortic outflow tract murmurs than a control group.

Many investigators have reported the pathologic and clinical features of patients with mitral anular calcification (MAC).[1–12] In particular, studies have stressed the older age of these patients and the high frequency of cardiac failure, heart murmurs, and conduction defects. Mention has been made of the marked distortion of the mitral anulus and mitral valve secondary to dense deposits of calcium in the anulus.[2,3] In autopsy series, the calcification is reported to extend several centimeters into the left atrial or left ventricular myocardium. Involvement of the conduction system and a high frequency of concomitant aortic root calcification have been noted.

The diagnosis of MAC has been simplified recently by echocardiography. Before echocardiography, chest roentgenography or cardiac fluoroscopy was used to establish an antemortem diagnosis of MAC. However, chest roentgenography is relatively insensitive in diagnosing MAC, and cardiac fluoroscopy is performed infrequently. Hence, data on MAC compiled before echocardiography were primarily obtained from autopsy series.

Several investigators have described the echocardiographic and clinical findings in patients with MAC.[5,7,8,10] However, their patients would be expected to have an increased frequency of heart murmurs, cardiomegaly, and conduction defects on the basis of older age, concomitant disease, aortic root calcification, or other cardiac disorders. Therefore, we compared the clinical and echocardiographic features of 104 patients with MAC with those of 121 age- and sex-matched control subjects.

Methods

We retrospectively reviewed for MAC all M-mode echocardiograms taken at the Creighton University Cardiac Center since 1974. Group 1 consisted of 104 consecutive patients with MAC detected by M-mode echocardiography. Group 2 con-

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TABLE I Clinical Data in Patients With MAC and in the Control Group

	104 Patients With MAC		121 Control Patients	
	n	%	n	%
Cardiomegaly on chest X-ray	87	84*	65	54
Echo chamber size				
Left atrial enlargement	48	46	45	37
Left ventricular enlargement	53	51	49	40
Heart murmur	89	86*	76	63
Aortic outflow tract murmur	67	64†	54	45
Aortic regurgitation murmur	10	10	11	9
Mitral stenosis murmur	7	7	4	3
Mitral regurgitation murmur	17	16	21	17
Diabetes mellitus	12	12	12	10
Hypertension	26	25	37	31
Coronary heart disease	30	29	48	40
Rheumatic heart disease	3	3	7	6

* $p < 0.001$.
† $p < 0.005$.

sisted of 121 patients without MAC determined by M-mode echocardiography selected as a control group. The control group was matched for age and sex with Group 1 patients without knowledge of any other clinical and laboratory information.

Of 104 patients with MAC, 53 (51%) were women and 51 (49%) men. Of 121 control patients, 62 (51%) were women and 59 (49%) men. The mean age of the patients with MAC was 70.5 ± 8.9 years and that of the control group 69.4 ± 8.3 years.

All M-mode echocardiograms were taken with a commercially available ultrasonograph using a 1.27 cm, 2.25 MHz, medium-focus transducer and a strip chart recorder. Posterior MAC was identified when a band of dense echoes was recorded anterior to the left ventricular posterior wall and moving parallel with it (Fig. 1). These echoes terminated at the atrioventricular junction and merged with the left ventricular posterior wall on echocardiographic sweep from the aortic root to the left ventricular apex. Anterior MAC was identified when a continuous band of dense echoes was noted at the level of the anterior mitral valve leaflet in both systole and diastole (Fig. 1). This echo-dense band was contiguous with the posterior wall of the aortic root. Aortic root calcification was identified when dense echoes were noted within the aortic root in both systole and diastole (Fig. 1). This finding was not necessarily associated with calcification or decreased excursion of aortic leaflets.

The heart murmurs were classified on the basis of auscultatory and phonocardiographic findings. A systolic ejection murmur recorded along the left sternal border or second right intercostal space was classified as an aortic outflow tract murmur. An apical holosystolic or late systolic murmur was classified as a mitral regurgitation murmur. A diastolic decrescendo murmur beginning with A_2 located along the right or left sternal border or at the apex was classified as an aortic regurgitation murmur. A mid-diastolic murmur at the apex with or without presystolic accentuation was categorized as a mitral stenosis murmur.

Chest roentgenograms in each patient were assessed for cardiomegaly.[13] Chamber enlargement by M-mode echocardiography in each patient was determined using previously described criteria.[14] Surface electrocardiograms in each patient were evaluated for conduction defects. Patients who had sinoatrial block, sinus arrest, or the tachycardia-bradycardia syndrome were classified as having sinoatrial disease. All measurements of heart size by chest roentgenography, echocardiographic measurements, and electrocardiographic interpretations were performed by us independently of knowledge of other clinical and laboratory information. The echocardiograms were read without knowledge of the electrocardiographic information and vice versa.

Statistical analyses were performed by our biostatistician using the chi-square test and Student's t test when appropriate.

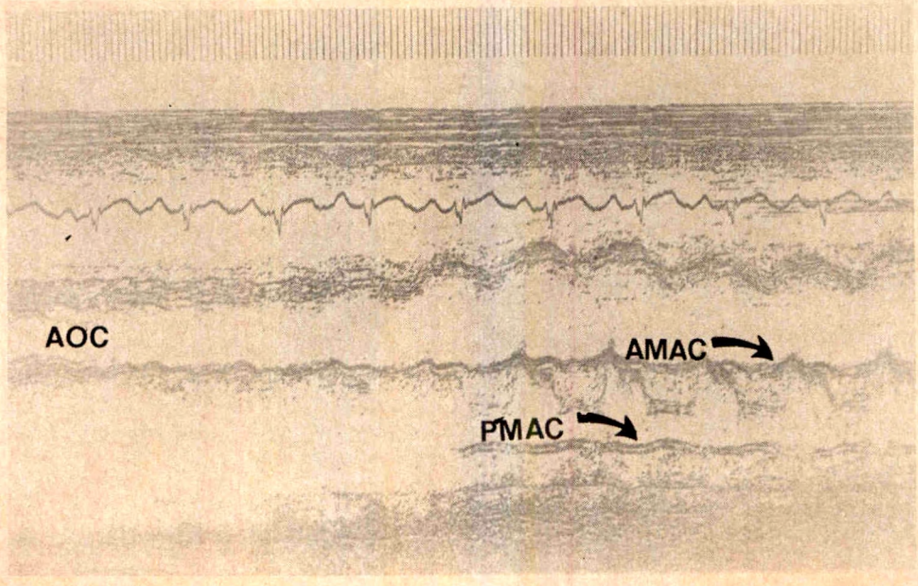

FIGURE 1. M-mode echocardiogram. Note the abrupt cephalad termination of posterior mitral anular calcification (PMAC). Anterior mitral anular calcification (AMAC) is continuous with posterior aortic root calcification (AOC).

TABLE II Incidence of Conduction Defects in Patients With MAC

Type of Calcification	n	Conduction Defect		Sinoatrial Disease		Atrioventricular Block		Bundle Branch Block, Left Anterior Hemiblock, or Intraventricular Conduction Defect	
		n	%	n	%	n	%	n	%
Anterior MAC	8	8	100	1	13	5	63*	6	75†
Posterior MAC	53	39	74	21	40	12	23	20	38
Anterior and posterior MAC	43	32	74	21	49	5	12	22	51
Total MAC	104	79	76	43	41	22	21	48	46
MAC with aortic root calcification	68	53	78	23	34	16	24	36	53
MAC without aortic root calcification	36	26	72	19	53	7	19	12	33

* $p < 0.025$ comparing anterior MAC with posterior MAC.
† $p < 0.05$ comparing anterior MAC with posterior MAC.

TABLE III Incidence of Conduction Defects in the Control Group

	n	Conduction Defect	
		n	%
Total group	121	44	36
Patients with aortic root calcification	20	8	40

Results

Table I contains clinical data on the 104 patients with MAC and the 121 control patients and any statistical differences. Table II shows the incidence of conduction defects in the subgroups of patients with MAC and any statistical differences. Sixty-eight patients with MAC had concomitant aortic root calcification, and 36 patients with MAC did not have aortic root calcification. Table III indicates the incidence of conduction defects in the 121 control patients and in the 20 control patients with aortic root calcification. No significant difference in the incidence of conduction defects occurred in the control patients with or without aortic root calcification.

Of 104 patients with MAC, 79 (76%) had conduction defects, compared with 44 (36%) of 121 control patients (chi-square = 35.39, $p < 0.001$). Twenty-six (72%) of 36 patients with MAC and without aortic root calcification had conduction defects, compared with 44 (36%) of 121 control patients with aortic root calcification (chi-square = 14.44, $p < 0.001$).

Forty (75%) of 53 women and 39 (76%) of 51 men with MAC had conduction defects. Seventeen (27%) of 62 women in the control group and 27 (46%) of 59 men in the control group had conduction defects (chi-square = 4.40, $p < 0.05$). A greater incidence of conduction defects occurred in women with MAC than in women in the control group (chi-square = 26.39, $p < 0.001$). A greater incidence of conduction defects occurred in men with MAC than in men in the control group (chi-square = 10.75, $p < 0.005$).

Discussion

On the basis of previous reports, M-mode echocardiography appears more sensitive than cardiac fluoroscopy in detecting MAC.[5,7,8,10] Anatomic studies have documented the correlation of location of calcification with specific conduction defects. However, to our knowledge, no previous echocardiographic study has evaluated the association between the different locations of MAC and the incidence and types of various conduction defects.

Previous studies have emphasized the greater incidence of MAC in women than in men. However, the incidence of MAC was similar in men and women in our study. This finding agrees with a previous report by Roberts and Perloff.[3]

Precordial murmurs are frequently described in patients with MAC. The greater incidence of heart murmur in our patients with MAC than in the control group was due to a higher incidence of aortic outflow tract murmurs.

Our study confirms previous reports that MAC is associated with conduction defects.[2,8–10,12] In our study this association was independent of age, sex, or conditions such as coronary artery disease, rheumatic heart disease, hypertension, or diabetes mellitus. A greater incidence of atrioventricular block and bundle branch block or left anterior hemiblock or intraventricular conduction defect was present in anterior MAC than in posterior MAC.

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Prosthetic Mitral Valve Motion During Cardiac Dysrhythmias As Determined by Echocardiography

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To assess the changes and physiologic mechanisms of prosthetic valve motion during cardiac dysrhythmias as well as the role of atrial systole in the closure of the mitral valve, M-mode echocardiography was performed in 36 patients with normally functioning prosthetic mitral valves (Björk-Shiley, Starr-Edwards, and Beall valve). Premature closure of the prosthetic mitral valve in diastole with a "sharp" closing motion was seen during first-degree atrioventricular block, atrial fibrillation with ventricular rates <60 beats/min, and atrial flutter. A "rounded" premature valve closure due to atrial systole was seen during atrial tachycardia and complete heart block. Atrial systole initiates a closing motion of the prosthetic mitral valve at end-diastole, and ventricular systole completes this closure during normal sinus rhythm. When first-degree atrioventricular block is present, atrial systole alone completes this closure before ventricular contraction. Atrial contraction alone also can effectively close the prosthetic mitral valve during atrial flutter and atrial tachycardia. Other factors (such as left ventricular diastolic volume) may play a role in the effective closure of the prosthetic mitral valve during atrial fibrillation with slow ventricular rates and complete heart block. These findings must be considered in the echocardiographic evaluation of suspected malfunctioning prosthetic mitral valves. A baseline postoperative echocardiogram after prosthesis insertion is important for future evaluation when clinically indicated.

The complex mechanics of mitral valve motion have been the subject of numerous studies[1–15] dating back to Baumgarten[1] in 1843. More recent echocardiographic studies of normal mitral valve motion have further enhanced our understanding of its function during normal and abnormal rhythms.[16–23] M-mode echocardiographic patterns of many of the various types of mitral prosthetic valves have also been described,[24–33] but the specific motion patterns during various cardiac dysrhythmias have not been elucidated.

This study details the effect of various rhythm and conduction disturbances on the M-mode echocardiographic motion pattern of the most commonly used, *normally functioning* prosthetic mitral valves, with special emphasis on the physiologic mechanisms of mitral valve closure.

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Methods

The study involved 36 patients (27 women and 9 men) with a mean age of 57 ± 8 (standard deviation [SD]) years. These persons had undergone isolated mitral valve replacement for a variety of disease entities (Table I). A Björk-Shiley tilting disc valve prosthesis was inserted in 26 patients, a Starr-Edwards caged-ball prosthesis in 6 and a Beall parallel (nontilting) moving disc valve in 4. No patient had signs or symptoms of a malfunctioning prosthetic mitral valve.

M-mode echocardiography was performed utilizing either a focused phased-array ultrasound system (Varian V-3000) in which an M-mode echocardiogram can be selected and recorded from a single arc of the 2-dimensional echo display, or utilizing an Advanced Technology Laboratories (Mark III) system with a 2.25 MHz transducer. Echocardiograms and electrocardiograms were simultaneously recorded on strip chart format using a paper speed of 50 mm/s.

The echocardiogram of the mitral valve prosthesis was taken with the transducer initially placed at the left parasternal border in the third or fourth intercostal space oriented perpendicularly to the chest wall. The orientation of the echo beam was adjusted in each instance to obtain the maximal excursion of the prosthetic valve. Patients with Starr-Edwards valves were examined with the transducer placed at the cardiac apex and directed up toward the left atrium, since the ball moves in a superior-inferior plane.

TABLE I Underlying Heart Disease, Type of Prosthetic Mitral Valve, and Cardiac Rhythm in 36 Patients (Mean Age 57 ± 8 Years) With a Mitral Valve Prosthesis

Case	Age (yr) & Sex	Heart Disease	Valve	Echoes Obtained in			
				NSR	AF	Atrial Flutter	Pacing
1	39F	RHD	B-S	2	2		
2	42F	RHD	B-S	1			
3	55F	RHD	B-S	2	1		
4	57F	RHD	B-S	1			
5	57M	MVP	B-S	2			
6	58M	RHD	B-S		2		
7	46F	RHD	B-S		1		
8	68F	RHD	B-S		1		
9	65M	RHD	B-S		1		
10	68F	CMA	B-S			(1 Atrial tachycardia)	
11	57F	RHD	B-S			1	1
12	57F	RHD	B-S			1	
13	57F	RHD	B-S		1		1
14	71F	RHD	B-S	1			1
15	54F	RHD	B-S				1
16	43F	RHD	B-S	(1 Complete heart block)			1
17	57M	RHD	B-S	1			
18	62F	RHD	B-S		1		
19	56F	RHD	B-S		1		
20	65F	RHD	B-S		1		
21	59F	RHD	B-S				1
22	58M	SBE	B-S		2		
23	69F	RHD	B-S		1		
24	56F	RHD	B-S		1		
25	61F	RHD	B-S	1		1	
26	57F	RHD	B-S	1			
27	47F	RHD	Beall		1		
28	71M	RHD	Beall		1		
29	42M	RHD	Beall	1			
30	63F	RHD	Beall	1			
31	58M	SBE	S-E		1		
32	69F	RHD	S-E		1		
33	58F	RHD	S-E		1		
34	47F	RHD	S-E	1			
35	61F	SBE	S-E		2		
36	54M	RHD	S-E		1		
Total				15	25	3	6

AF = atrial fibrillation; B-S = Björk-Shiley prosthetic valve; CMA = calcified mitral anulus; MVP = mitral valve prolapse; NSR = normal sinus rhythm; RHD = rheumatic heart disease; SBE = subacute bacterial endocarditis; SD = standard deviation; S-E = Starr-Edwards prosthetic valve.

Each patient had 1 to 4 separate M-mode echocardiograms from 1 day to 15 years after mitral valve replacement. Normal sinus rhythm was present in 15 studies, atrial fibrillation in 25 studies, atrial flutter in 3 studies, and atrial tachycardia in 1 study (Table I). In addition, echocardiographic studies were performed during various modes of cardiac pacing (2 ventricular, 2 atrioventricular sequential, and 2 atrial pacing). In 1 patient with mitral and aortic valve replacement and underlying complete heart block, M-mode echocardiograms were obtained with various heart rates using temporary ventricular pacing.

Measurements: In all patients, the heart rate was expressed as the R-R interval in milliseconds (ms), and the longest and shortest R-R interval of each echocardiographic study was noted in patients with atrial fibrillation. The Q-C interval in milliseconds was measured from the onset of the QRS complex to the point of complete closure of the prosthetic mitral valve at end-diastole. The P-R interval was expressed in milliseconds. Differences in groups were assessed by the 2-tailed Student's t test. The values reported represent means ± standard deviation.

Results

M-mode echocardiographic patterns of various types of normally functioning mitral prosthetic valves: A characteristic M-mode echocardiographic motion pattern was observed for each type of mitral prosthetic valve. The Björk-Shiley tilting disc valve (26 patients) demonstrated an early diastolic rapid upward opening motion of the disc which maintained an open position throughout diastole and was followed by a brisk downward closing motion at the end of diastole. The edges of the disc are peaked and can be clearly seen on the M-mode echocardiographic recordings (Fig. 1). The Starr-Edwards ball valve (6 patients) showed round edges and a more gradual opening and closing motion; its diastolic motion resembles the echocardiographic pattern of mitral stenosis (Fig. 2). The Beall disc valve (4 patients) demonstrated a gradual opening and closing motion with sharp, clearly defined edges of the disc and a smaller amplitude of excursion.

Echocardiographic features of the mitral prosthetic valves during dysrhythmia: No significant difference in the echocardiographic motion pattern and closure between the various types of prosthetic valves were seen during dysrhythmia. Thus, the following findings during different arrhythmias were similar for each individual type of valve prosthesis.

Normal sinus rhythm: Fifteen M-mode echocardiograms of prosthetic mitral valve were obtained during normal sinus rhythm (NSR) in which the mean R-R interval was 791 ± 99 ms.

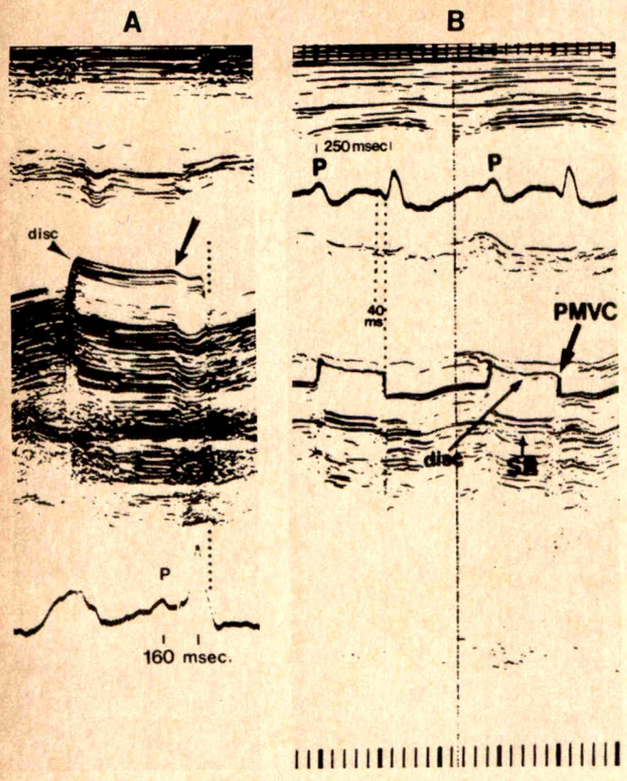


FIGURE 1. Björk-Shiley tilting disc valve in mitral position during sinus rhythm with normal (**A**) and prolonged P-R interval (**B**) is shown. A brisk opening and closing motion of the disc with sharp edges are seen. **A,** a late diastolic "hump" (**large arrow**) corresponding with the atrial contraction (P wave) is noted during sinus rhythm with P-R interval of 160 ms, and the Q-C interval is 70 ms (**dotted line**). **B,** during a prolonged P-R interval of 250 ms, premature mitral valve closure (PMVC) is noted with a Q-C interval of 40 ms (**between dotted lines**). SR = sewing ring.

A late diastolic anterior motion ("hump") on the prosthetic mitral valve echocardiogram was observed in NSR induced by atrial contraction (Fig. 1A).

In 10 of the 15 echocardiographic studies during normal sinus rhythm (mean R-R interval 792 ± 76 ms) the P-R interval was normal (mean 167 ± 18 ms, range 140 to 195). In this group, the Q-C interval was 60 to 80 ms (mean 68 ± 7) (Fig. 1A and 3).

In 5 other studies with a mean R-R interval of 788 ± 146 ms, the P-R interval was prolonged (mean 284 ± 82 ms, range 200 to 390). In this group, the prosthetic valve closed earlier; the Q-C interval was always ≤60 ms (range 20 to 60, mean 40 ± 18) ($p < 0.001$) (Fig. 1B and 3). In general, the longer the P-R interval, the earlier the prosthetic mitral valve closed during end-diastole. No patient had evidence of acute severe aortic regurgitation.

Atrial fibrillation: Twenty-five M-mode echocardiographic studies of various prosthetic mitral valves were obtained during atrial fibrillation. Due to the lack of atrial systole, no diastolic "humps" on the prosthetic mitral valve could be observed. After the initial opening motion, the prosthetic mitral valve maintained an open position throughout diastole (Fig. 2). In 1 patient, however, with R-R interval of 850 ms, partial closure in mid-diastole and reopening was seen.

The shortest and longest R-R intervals in each study and the corresponding Q-C interval in milliseconds were measured. In all types of prosthetic valves, during longer R-R intervals (slow ventricular rates), the valve closed earlier than in cases in which the R-R intervals were shorter (faster ventricular rates) (Fig. 4). In 13 studies with R-R intervals >1,000 ms, mean 1,190 ± 167, the Q-C interval was always ≤70 ms, mean 63 ± 8, and decreased to 45 ms with the longest R-R interval of 1,520 ms (Fig. 2A and 4).

In 37 studies with R-R intervals <1,000 ms (mean 665 ± 169), the Q-C interval was always ≥70 ms (mean 80 ± 11) ($p < 0.001$) and increased to 105 ms with the shortest R-R interval of 400 ms (Fig. 2B and 4).

Atrial flutter: Three patients with a Björk-Shiley mitral prosthesis were studied during atrial flutter. In these 3 studies (1 with 2:1 atrioventricular block and 2 with 4:1 atrioventricular block) the R-R interval was 500 to 750 ms and the Q-C interval 60 to 70 ms. The prosthetic mitral valve remained open throughout diastole in 2 of the 3 studies. In 1 study with an atrial rate of 240 beats/min during a sudden change in the atrioventricular conduction ratio from 2:1 to 3:1, a mid-diastolic closing of the prosthetic valve was followed by reopening of the valve in late diastole by the following atrial contraction (F wave) (Fig. 5).

Atrial tachycardia: One patient with an atrial rate of 220 beats/min had variable atrioventricular block. The Björk-Shiley prosthetic valve demonstrated partial or complete early diastolic closure. Subsequent late diastolic P waves were followed by reopening of the prosthetic valve, which closed at the onset or end of QRS complex, but always 140 ms from the peak of the preceding P wave (Fig. 6). Hence, the onset of systole did not initiate mitral valve closure. A rounded opening and closing motion of the prosthetic valve was observed whenever this motion was induced by atrial systole (Fig. 6).

Pacing studies: Six echocardiographic studies of the Björk-Shiley prosthetic mitral valve were obtained in various modes of cardiac pacing and the differences of the echocardiographic motion pattern and closure of the prosthetic valve in these modes of pacing were examined.

Ventricular pacing: In 1 of the 2 studies with ventricular pacing, the underlying atrial rhythm was atrial fibrillation. The cycle length was 1,050 ms and the diastolic mitral valve opening was of constant duration at a fixed rate of ventricular pacing. The prosthetic valve remained open throughout diastole and closed 80 ms after the onset of the QRS complex.

In 1 patient with underlying complete heart block, the motion of the Björk-Shiley valve was recorded during various rates of ventricular pacing (Fig. 7, top and center). When the ventricular pacing was turned off, the motion of the Björk-Shiley mitral valve was recorded during complete heart block with junctional rhythm and similar phenomena were observed as shown and described in Figure 7 (bottom).

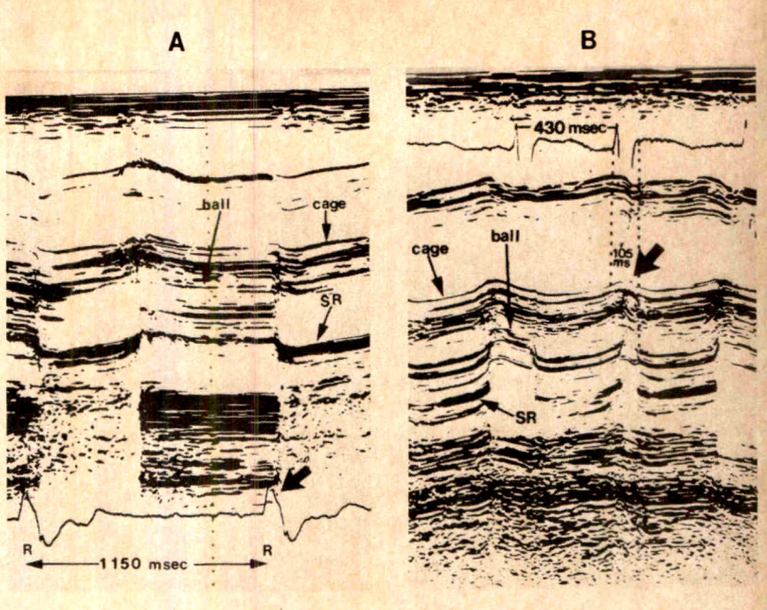


FIGURE 2. Starr-Edwards ball-cage valve in mitral position during atrial fibrillation with slow (**A**) and rapid ventricular response (**B**) is shown. The round edges of the valve are noted. **A,** the Q-C interval during the long R-R interval (1,150 ms) is 65 ms (**large arrow**). **B,** the Q-C interval is 105 ms (**between dotted lines**) during the short R-R interval (430 ms) (**large arrow**). SR = sewing ring.

A diastolic notch on the prosthetic mitral valve corresponding to the atrial contraction (P wave) was seen in these studies (Fig. 7). A rounded closing motion of the prosthetic mitral valve was observed during the atrial systole-induced closure of the valve, while the closing motion of the valve was sharp when the ventricular systole completed the prosthetic valve closure (Fig. 7).

Atrial pacing: The 2 patients with Björk-Shiley valve and atrial pacing had a prolonged atrioventricular conduction time (360 and 380 ms, respectively); as expected, the prosthetic valve remained open throughout diastole and closed early at end-diastole, 40 ms after the onset of QRS complex.

Atrioventricular pacing: One of the 2 patients with Björk-Shiley valve and atrioventricular sequential pacing had a prolonged atrioventricular interval of 270 ms; the prosthetic valve sometimes demonstrated premature closure at end-diastole before the onset of QRS complex, or partial closure in mid-diastole and reopening at end-diastole.

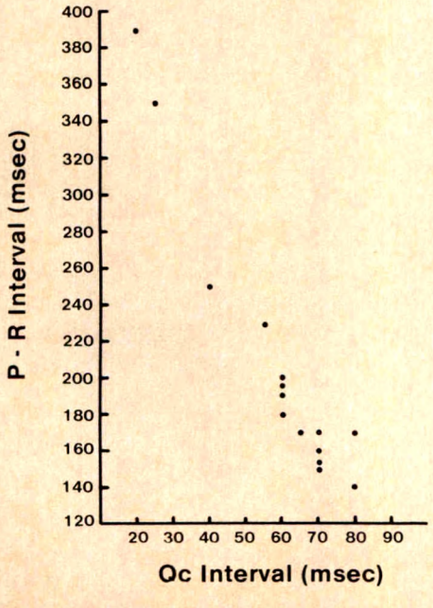


FIGURE 3. Relation between the P-R interval (**ordinate**) and onset of QRS to closing point of the prosthetic valve interval (Q-C interval) (**abscissa**) is shown during sinus rhythm. Note the earlier mitral valve closure with prolongation of the P-R interval.

Discussion

This and previous echocardiographic studies have described the motion of the most commonly used, normally functioning prosthetic valves in the mitral position.[24–33] These echocardiographic patterns can identify which type of valve is imaged and determine possible valve malfunction. Signs of malfunction described include clot formation around the valve,[34–36] rounded and slowed pattern of opening and closure,[37–40] or intermittent, delayed, or incomplete opening of the valve[40–43] due to clot formation, and early diastolic "hump" due to perivalvular leak.[37,44,45]

Cardiac arrhythmias can also influence the normal echocardiographic pattern of the prosthetic valves and result in altered motion patterns, which may mimic some of the echocardiographic signs of malfunctioning prosthetic valve. In the present study we describe the specific M-mode echocardiographic motion patterns and closure characteristics of mitral prosthetic valves during various cardiac dysrhythmias, emphasizing the physiologic mechanisms of their closure.

There was no difference between the various types of artificial prosthetic valves in the motion and closure characteristics induced by dysrhythmias; thus, our observed findings apply to each type of prosthesis.

Effect of the P-R interval on mitral closure pattern: The normal interval from the onset of the QRS

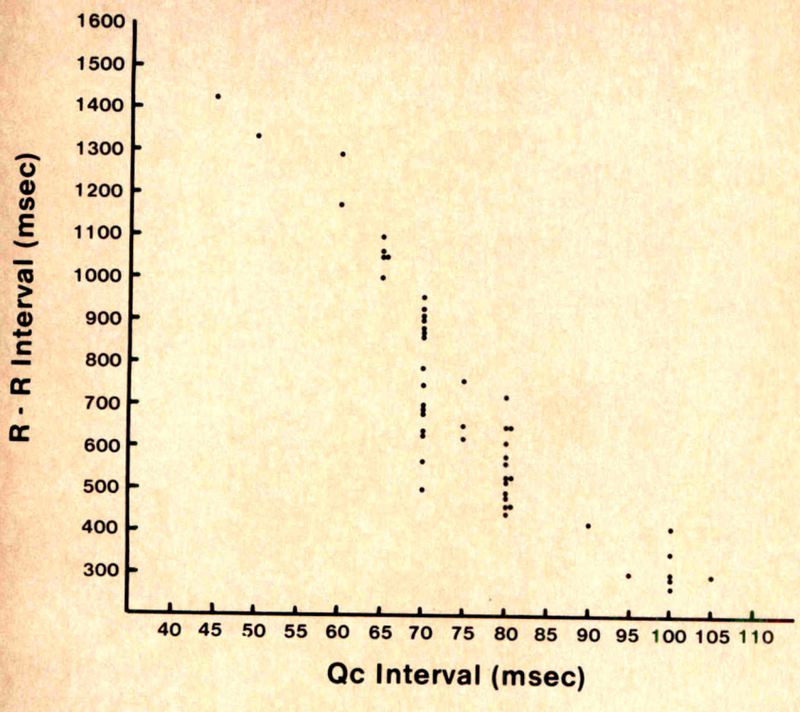


FIGURE 4. Relation between the R-R interval (**ordinate**) and onset of QRS to closing point of the prosthetic valve interval (Q-C interval) (**abscissa**) is shown during atrial fibrillation. Note the earlier mitral valve closure with long R-R intervals (slower ventricular rates).

complex to the onset of left ventricular systole is 52 ms.[46] Pohost et al[20] described a good correlation between the echocardiographically defined mitral valve closure and the hemodynamic indicators of its closure. The onset of left ventricular systole occurred 25 ± 10 ms before the termination of the final rapid posterior motion of the mitral valve by echocardiography. The normal interval from the onset of the QRS complex to the echocardiographic closure of the mitral valve is 77 ± 10 ms.[20,46] Other studies[22,47] reported an average QRS-to-closure click interval of 63 to 73 ms during sinus rhythm with normal P-R interval in patients with normally functioning Starr-Edwards mitral valve prostheses. We found a similar mean Q-C interval of 68 ± 7 ms (SD) by M-mode echocardiography in patients with various prosthetic mitral valves, most commonly Bjork-Shiley type, who were in sinus rhythm with a normal P-R interval (Fig. 3).

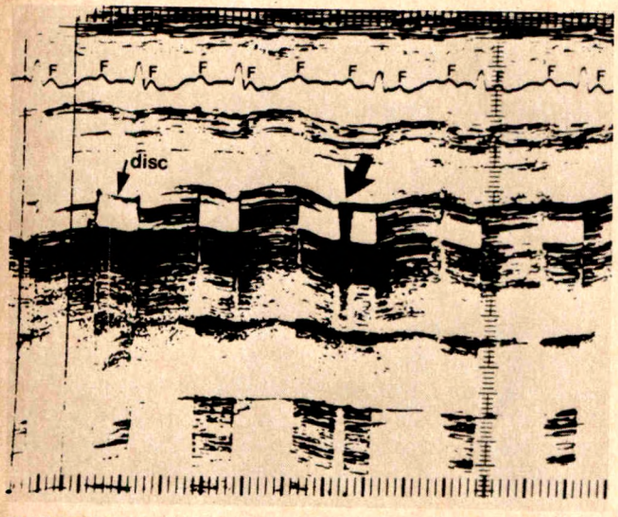


FIGURE 5. Björk-Shiley prosthetic valve in mitral position during atrial flutter with 2:1 atrioventricular block is shown. During a sudden change in the atrioventricular conduction ratio from 2:1 to 3:1 (**large arrow**), the prosthetic valve closes in mid-diastole and is reopened in late diastole by the following atrial contraction (F = flutter wave). Note the abrupt opening and closing motion of the valve. The Q-C interval is 60 ms.

It appears, therefore, that during sinus rhythm with normal P-R interval, the hemodynamics of closure of a prosthetic mitral valve are similar to those of the normal mitral valve, influenced directly by the left ventricular-left atrial pressure gradient and mitral valve flow.[4–6,8,9] Atrial systole results in an augmentation of the left ventricular pressure and initiates the closure of the prosthetic mitral valve. Valve closure is then completed by the pressure developed by left ventricular contraction.[10,14,15,22]

A late diastolic "hump" on the prosthetic mitral valve echocardiogram was frequently observed, corresponding to the P wave on the electrocardiogram (Fig. 1A), representing the effect of atrial contraction. This late diastolic "hump" should be distinguished from the early diastolic "hump" on a prosthetic valve, which may indicate a perivalvular leak[37,44,45] or clot formation,[39] and from an early diastolic notch on a Beall[48] or Starr-Edwards valve indicating valve variance.

Premature mitral valve closure in first-degree atrioventricular block has been demonstrated by several experimental[14,16,19] and clinical studies of the normal[49] or prosthetic mitral valve.[22,50–52] Zaky et al[16] showed complete or incomplete presystolic mitral valve closure in patients with a P-R interval ≥180 ms. We also observed that in the presence of sinus rhythm with a P-R interval ≥200 ms, the prosthetic mitral valve closed

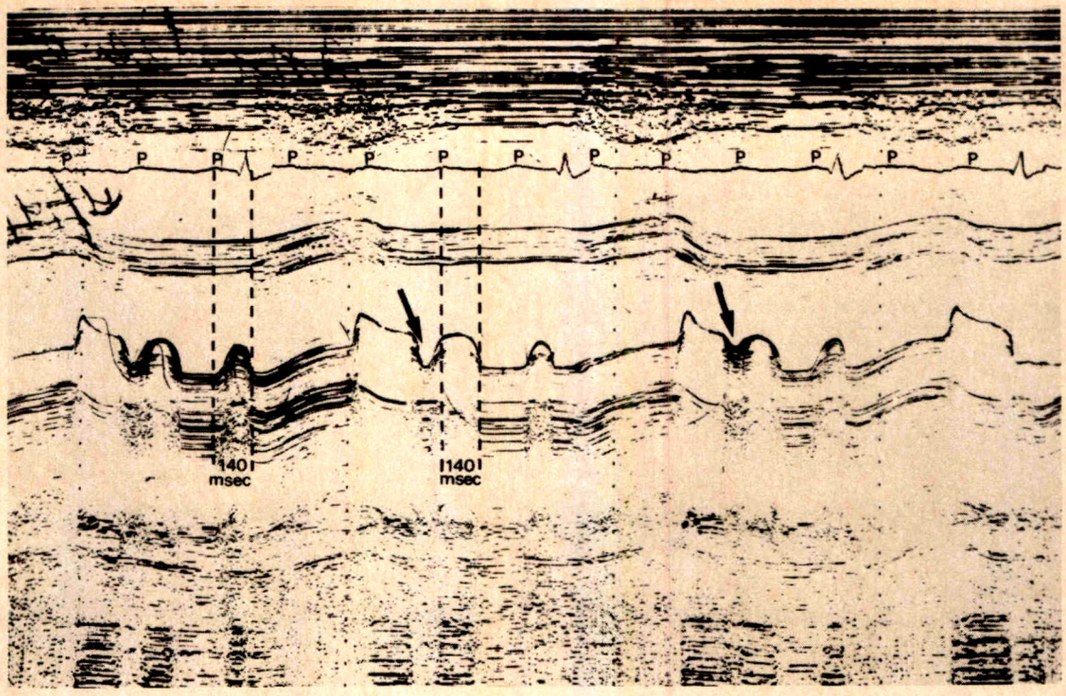


FIGURE 6. Björk-Shiley prosthetic valve in mitral position is shown during atrial tachycardia with variable atrioventricular block demonstrating partial or complete closure in early diastole (**arrows**) and reopening of the valve by subsequent late diastolic P waves. The valve closes consistently 140 ms from the peak of the preceding P wave. Notice the rounded opening and closing motion induced by the atrial systole.

earlier at end-diastole with a mean Q-C interval of 40 ± 18 ms ($p < 0.001$) (Fig. 1B); the Q-C interval shortened as the P-R interval lengthened (Fig. 3).

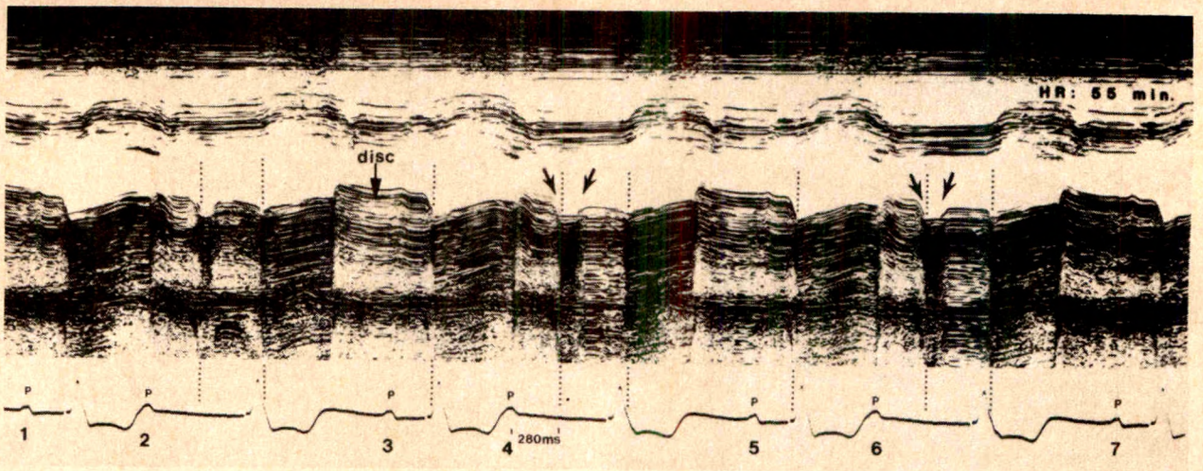
The prolonged atrioventricular conduction permits the atrial contraction to influence the closure of the prosthetic valve before the ventricle contracts. Thus, a mid-diastolic reversal of the mitral flow and a ventriculoatrial pressure gradient induced by the atrial systole results in premature, partial, or complete valve closure before the onset of ventricular contraction[5,8,16,19] and possible presystolic mitral regurgitation.[14]

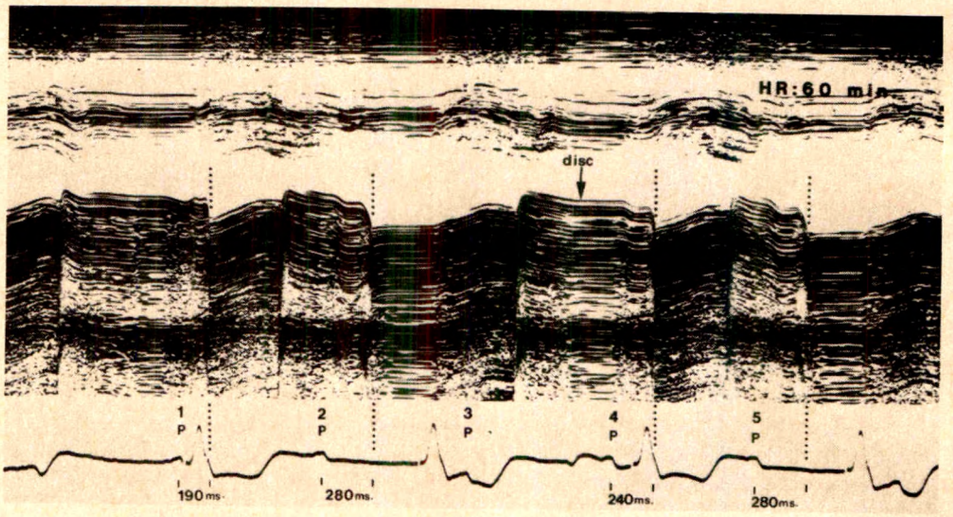
The hemodynamic consequences of this premature valve closure in first-degree atrioventricular block are not well known. Williams and Wood[53] observed that there is an optimal P-R interval, varying with heart rate, beyond which stroke volume and systolic pressure tend to decrease. Moreover, it is clinically important to recognize the occurrence of the premature prosthetic valve closure in first-degree atrioventricular block, since this phenomenon has also been observed in patients with prosthetic mitral valve and acute severe aortic regurgitation.[54,55]

Atrial fibrillation: Several experimental studies of the hemodynamic effects of atrial fibrillation suggested that mitral regurgitation may occur as a result of atrial fibrillation with relatively slow ventricular rates.[23,56–58] The motion of the normal and prosthetic mitral valve during atrial fibrillation has also been studied by M-mode echocardiography.[22,59–61] In patients with Starr-Edwards valves and atrial fibrillation, Hamby et al[22] found an average QRS-to-closure click interval of 86 ± 5 ms, determined by phonocardiography. An inverse relation between the length of the preceding R-R cycle and the Q-C interval of the prosthetic mitral valve has been demonstrated in atrial fibrillation.[49,62–64] We also observed that with R-R intervals >1,000 ms (ventricular rates <60 beats/min), the Q-C interval was always ≤70 ms, mean 63 ± 8 (Fig. 2A and 4). In contrast with R-R intervals <1,000 ms (ventricular rates >60 beats/min), the Q-C interval was always ≥70 ms, mean 80 ± 11 ms ($p < 0.001$) (Fig. 2B and 4).

These findings demonstrate that in atrial fibrillation, in which the effect of atrial systole is lost, the closure of the prosthetic mitral valve is due to the ventricular contraction when the ventricular response of atrial fibrillation is >60 beats/min. On the other hand, with ventricular rates <60 beats/min, the closure of the prosthetic mitral valve is not accomplished by the ventricular contraction. The mechanism of this early closure of the prosthetic mitral valve during atrial fibrillation with prolonged filling periods may be associated with an increment in left ventricular pressure, resulting in a ventriculoatrial gradient across the mitral valve or the development of a critical left ventricular volume—the "locking" volume—adequate to close the valve without ventricular contraction.[23] Another explanation may be due to the reflection of incoming jets of blood off the apex of the left ventricle during early diastole resulting in ring vortex formation and premature closure of the mitral valve, and the effect of gravity reported in all valve prostheses.[65]

Atrial flutter: The echocardiographic motion pattern of the normal mitral valve in atrial flutter has been described,[59,60,66–68] but only in 2 patients with a pros-





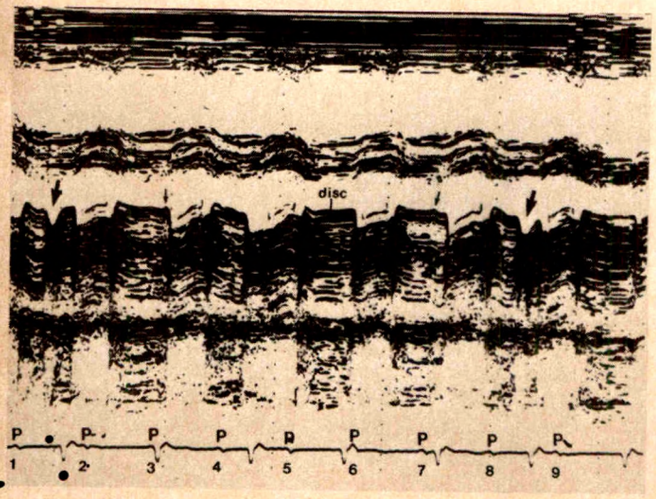


FIGURE 7. Björk-Shiley prosthetic valve in mitral position is shown during complete heart block and various rates of ventricular pacing. **Top,** at a pacing rate of 55 beats/min, the prosthetic valve closes in mid-diastole with a rounded motion (**arrows**) 280 ms after the peak of a P wave occurring early in diastole with a P-R interval of 650 ms (second, fourth, and sixth P waves) and reopens in late diastole to be closed 80 ms after the onset of QRS complex. When the P wave occurs late in diastole with a P-R interval of 290 ms (first, third, fifth, and seventh P waves), the prosthetic valve remains open throughout diastole and closes at the onset of QRS complex, 280 ms after the peak of the P wave. **Center,** at a pacing rate of 60 beats/min, the prosthetic valve closes in mid-diastole with a round motion, 280 ms after the peak of P waves (second and fifth P waves) occurring early in diastole (P-R interval 600 and 580 ms, respectively), but does not reopen during the rest of diastole. When the P waves occur late in diastole (first and fourth P waves) with P-R intervals 120 and 200 ms, respectively, the prosthetic valve remained open throughout diastole and was closed by ventricular systole with an abrupt motion 80 ms after the onset of QRS complex. **Bottom,** a Björk-Shiley prosthetic valve in mitral position is shown during complete heart block. With a P-R interval of 60 ms (third P wave) and 160 ms (seventh P wave), the prosthetic valve remains open throughout diastole and closes 70 ms after the onset of QRS complex. A diastolic notch is seen on the prosthetic valve (**small arrows**) corresponding to atrial contraction. With further increase in the P-R interval to 300 ms (fourth P wave), the valve closes prematurely in late diastole before the onset of QRS complex. When the P wave occurs earlier in diastole (first and eighth P waves) with P-R intervals 440 and 400 ms, respectively, the valve closes in mid-diastole and reopens (**large arrows**) to be closed 70 ms after the onset of QRS complex. With even longer P-R intervals (second, fifth, and ninth P waves) of 660, 520, and 640 ms, respectively, the valve remains open throughout diastole and closes 70 ms after the onset of QRS complex.

thetic mitral valve (Starr-Edwards ball valve).[60,67] In 1 patient with Björk-Shiley mitral valves, mid-diastolic closure of the prosthetic mitral valve was observed after a flutter wave with reopening in late-diastole during a sudden change of the atrioventricular conduction ratio from 2:1 to 3:1 (Fig. 5). This early diastolic closure of the mitral valve during atrial flutter with >2:1 atrioventricular block also has been observed by others in normal subjects[59,66] and in patients with prosthetic mitral valve.[60] Flutter waves, therefore, can generate an effective atrial contraction which opens and then closes the prosthetic mitral valve by raising the left ventricular diastolic pressure and reversing the atrioventricular pressure gradient.[60] Due to the shortened diastolic time, the atrial-induced early diastolic closure of the mitral valve is not seen during atrial flutter with 2:1 atrioventricular conduction (Fig. 5).

Atrial tachycardia: There have been only a few echocardiographic case reports of the motion of the normal mitral valve during supraventricular tachycardias.[68–70] We observed a unique echocardiographic motion pattern of the Björk-Shiley prosthetic mitral valve in atrial tachycardia with varying atrioventricular block (Fig. 6). The prosthetic mitral valve closed partially or completely in early diastole and was subsequently opened and closed with a rounded motion by the following P waves independently from the ventricular contraction (Fig. 6), in contrast to atrial flutter where the opening and closing motion of the prosthetic valve was sharp (Fig. 5).

This demonstrates that atrial contraction induced by the atrial tachycardia P waves can also effectively open and close the prosthetic mitral valve without the contribution of the ventricular systole.

Paced rhythm: Two patients with Björk-Shiley mitral valve and atrial pacing with prolonged atrioventricular conduction demonstrated, as expected, premature closure of the prosthetic valve at end-diastole, 40 ms after the onset of QRS complex. One patient, however, with atrioventricular sequential pacing and prolonged atrioventricular interval demonstrated incomplete closure and reopening or premature closure at end-diastole, but always before the onset of the QRS complex. This difference in closure characteristics in these 2 modes of pacing is not clearly understood.

On the other hand, in a patient with ventricular pacing and underlying atrial fibrillation, the prosthetic mitral valve remained open throughout diastole and was closed by ventricular systole. In another patient with Björk-Shiley valve and underlying complete heart block, the motion of the prosthetic mitral valve was recorded at various ventricular pacing rates and off pacing (Fig. 7). Atrial systole coincident with early diastolic P waves induces a rounded mid-diastolic closing motion of the prosthetic valve which may reopen in late diastole and finally be closed at end-diastole by the ventricular systole with a sharp closing motion (Fig. 7, top and center). This patient had symptoms of dizziness and hypotension (so-called "pacemaker syndrome"), probably due in part to premature mitral valve closure from early occurring P waves in diastole. Similar phenomena were observed with the pacemaker turned off with complete heart block being present (Fig. 7, bottom). These findings are in agreement with other echocardiographic studies of patients with complete heart block and normal mitral valve[16,21] which demonstrated that with prolonged P-R intervals there was early closure and reopening of the mitral valve in diastole and secondary closure initiated by ventricular systole.

The hemodynamic effects of cardiac pacing have been examined in animal studies utilizing echocardiography[71] but not in humans. The importance of a physiologic atrioventricular sequencing during cardiac pacing has been shown[72] and our findings demonstrate the potential application of M-mode echocardiography in the evaluation of patients with various pacing modes and symptoms of the "pacemaker syndrome."

Although our study is retrospective, our findings provide important morphologic, physiologic, and clinical information in patients with prosthetic mitral valves during various cardiac dysrhythmias and should be considered in the echocardiographic evaluation of suspected malfunctioning prosthetic mitral valves. We recommend baseline postoperative echocardiograms in all patients with prosthetic mitral valves so that more information can be obtained from repeat studies when clinically indicated.

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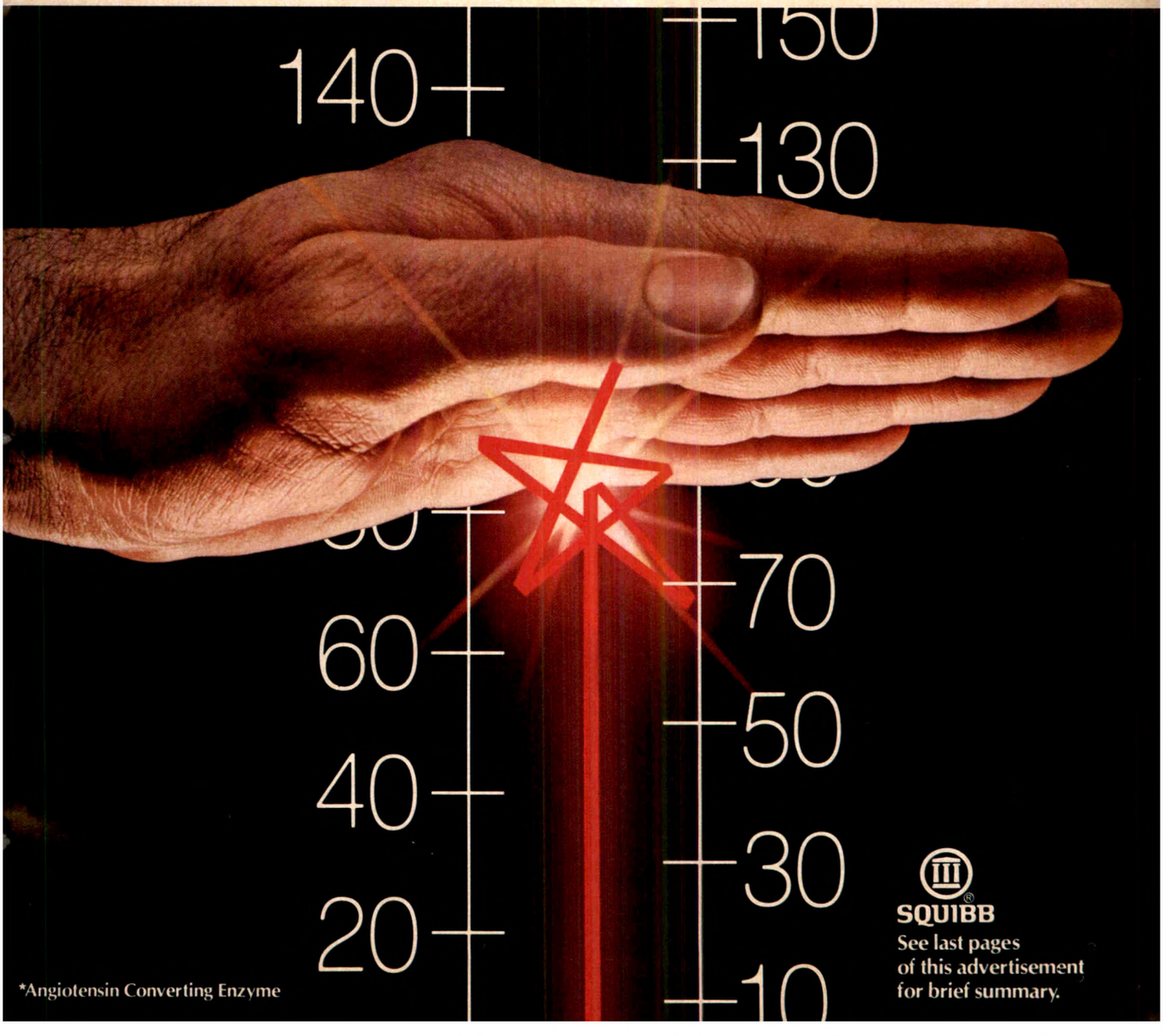

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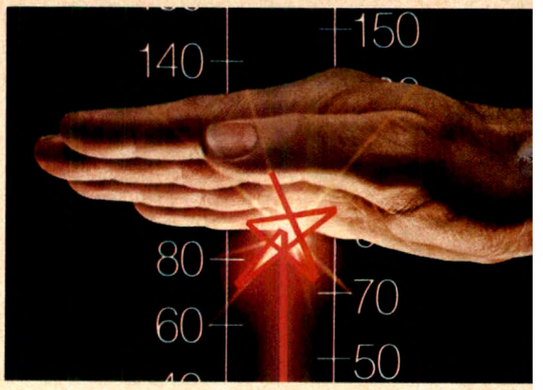

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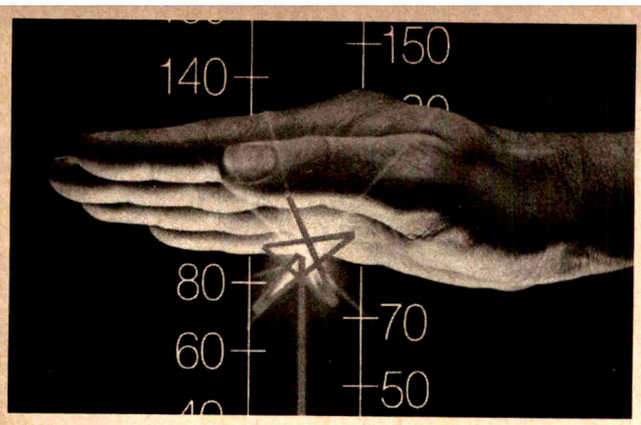

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CAPOTEN has been associated with the development of neutropenia, agranulocytosis, or proteinuria.† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

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CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.
Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.
PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.
Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.
Agents Causing Renin Release — Captopril's effect will be augmented by

(Continued on next page.)

(continued from preceding page)

antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

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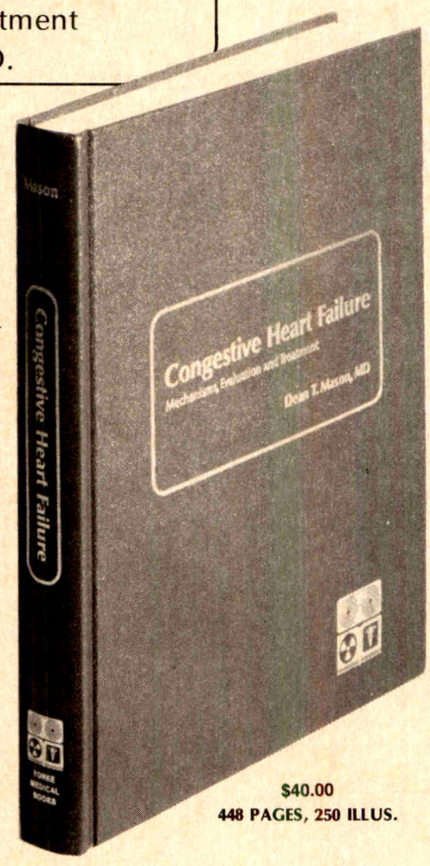
Congestive Heart Failure

Mechanisms, Evaluation and Treatment

Dean T. Mason, M.D.



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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis. President, Western Society for Clinical Research

Immediate Past President, American College of Cardiology

Member of the American Board of Internal Medicine Cardiovascular Diseases

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Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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Morphologic Features of the Normal and Abnormal Mitral Valve

WILLIAM C. ROBERTS, MD

Anatomic and functional features of the normal and abnormal mitral valve are reviewed. Of 1,010 personally studied necropsy patients with severe (functional class III or IV, New York Heart Association) cardiac dysfunction from primary valvular heart disease, 434 (43%) had mitral stenosis (MS) with or without mitral regurgitation (MR): unassociated with aortic valve stenosis or regurgitation or with tricuspid valve stenosis in 189 (44%) patients, and associated with aortic stenosis in 152 (35%), with pure (no element of stenosis) aortic regurgitation in 65 (15%) patients, and with tricuspid valve stenosis with or without aortic valve stenosis in 28 (6%) patients. The origin of MS was rheumatic in all 434 patients. Of the 1,010 necropsy patients, 165 (16%) had pure MR (papillary muscle dysfunction excluded): unassociated with aortic valve stenosis or regurgitation or with tricuspid valve stenosis in 97 (59%) patients, and associated with pure aortic regurgitation in 45 (27%) and with aortic valve stenosis in 23 (14%) patients. When associated with dysfunction of the aortic valve, pure MR was usually rheumatic in origin, but when unassociated with aortic valve dysfunction it was usually nonrheumatic in origin. Review of operatively excised mitral valves in patients with pure MR unassociated with aortic valve dysfunction disclosed mitral valve prolapse (most likely an inherent congenital defect) as the most common cause of MR. Excluding the patients with MR from coronary heart disease (papillary muscle dysfunction), mitral prolapse was the cause of MR in 60 (88%) of the other 68 patients, and a rheumatic origin was responsible in only 3 of the 68 patients, all 68 of whom were >30 years of age.

Mitral anular calcification in persons aged >65 years is usually associated with calcific deposits in the aortic valve cusps and in the coronary arteries. Because calcium in each of these 3 sites is common in older individuals residing in the Western World, it is most reasonable to view mitral anular calcification in older individuals as a manifestation of atherosclerosis. Mitral anular calcium appears to be extremely uncommon in persons with total serum cholesterol levels <150 mg/dl. Mitral anular calcium may produce mild MR and, if the deposits are heavy enough, MS.

This report reviews anatomic findings in both the normally and abnormally functioning mitral valve. Major attention is directed to anatomic observations which have clinical usefulness. This review focuses primarily on studies carried out in my laboratory during the past 20 years.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received and accepted December 3, 1982.

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Normal Mitral Valve (Fig. 1)

The mitral valve, in comparison with the semilunar valves, is a complex structure consisting of 4 major components: leaflets, chordae tendineae, papillary muscles, and anulus.[1,2] Unlike the other 3 cardiac valves, each of which has 3 cusps, the mitral valve consists of only 2 *leaflets*. The anterior one has a much longer basal-to-margin length than does the posterior leaflet, but the length of the anular attachment of the posterior leaflet (about 6 cm) is about twice that of the anterior leaflet (about 3 cm) (Fig. 1). Although the basal-to-margin lengths and the lengths of the basal attachments

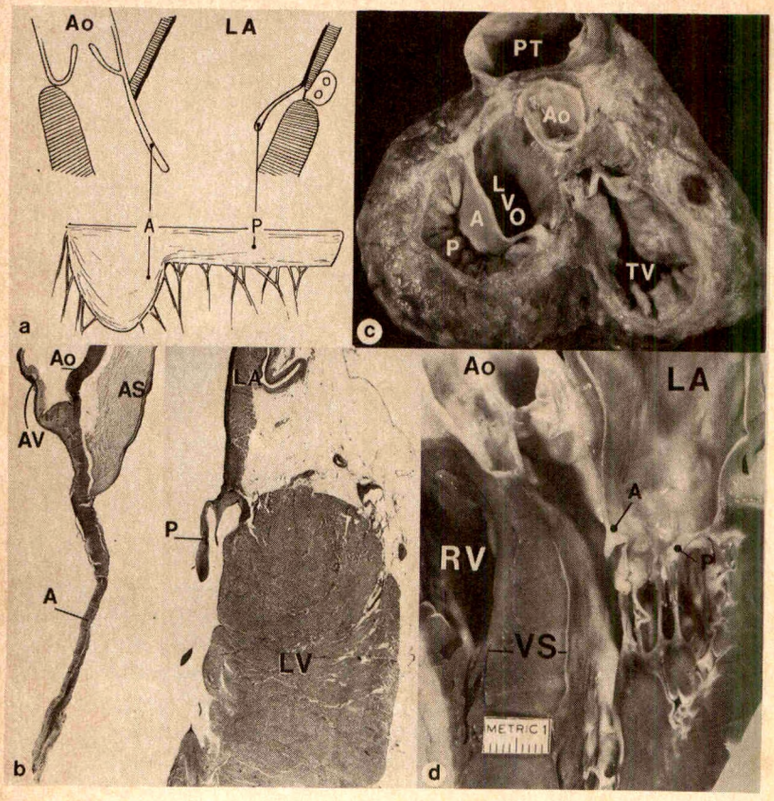

FIGURE 1. Normal mitral valve. **a,** diagram showing relation of anterior (A) and posterior (P) mitral leaflets to one another and to left atrium (LA), aortic valve (AV), and aorta (Ao). The inflow and outflow tracts of the left ventricle are divided by the anterior leaflet. The basal attachment of the posterior leaflet is twice as long as that of the anterior leaflet, although the basal-to-margin length of the anterior leaflet is twice that of the posterior leaflet. **b,** histologic sections of the mitral valve confirming the observations depicted in **a.** One section includes the anterior (A) mitral leaflet, the aortic valve cusp (AV), the wall of the aorta (Ao), and the atrial septal (AS) wall, and the other includes the left atrial and left ventricular free walls with intervening posterior mitral leaflet. (Elastic van Gieson stains; magnification ×4.5 and ×3, reduced 45%). **c,** view of the heart from above after excision of the atria. The anterior (A) mitral leaflet separates the left ventricular inflow from outflow (LVO). PT = pulmonary trunk; TV = tricuspid valve. **d,** longitudinal cut of the left ventricle, mitral valve, aorta, and left atrium, as would be seen by M-mode echocardiogram.

of each mitral leaflet are quite different, the surface area of each leaflet is virtually identical. The posterior leaflet has a true bundle of fibrous tissue (the anulus) separating the myocardium of left atrium from the myocardium of left ventricle. The posterior leaflet, in a large sense, is simply an extension of mural endocardium from the free walls of the left atrium. In contrast to the posterior mitral leaflet, the anterior leaflet does not have a true anulus but is continuous with the wall of the ascending aorta, aortic valve, membraneous ventricular septum, and atrial septum. The area of the leaflets is about 2.5 times that of the area of the mitral orifice at the level of the mitral anulus. In contrast to the semilunar cusps, which are independent or discontinuous of each other, the 2 mitral leaflets are continuous with each other, being connected at the commissures.

Chordae tendineae from both mitral leaflets insert into both papillary muscles. About 5 times as many

TABLE I Functional and Anatomic Classification of Valvular Heart Disease in 1,010 Necropsy Patients Aged ≥15 Years*

Functional Class	Patients (n [%])	Anatomic Class (n [%])				
		AV	MV	MV-AV	TV-MV	TV-MV-AV
1. Aortic stenosis (AS)	292 (29)	256 (87.5)	0	35 (12.1)	0	1 (0.3)
2. Mitral stenosis (MS)	189 (19)	0	117 (62)	40 (21)	13 (7)	19 (10)
3. MS + AS	152 (15)	0	0	120 (79)	0	32 (21)
4. Aortic regurgitation (AR)	119 (12)	107† (90)	0	10 (8)	0	2 (2)
5. Mitral regurgitation (MR)	97 (10)	0	85 (88)	8 (8)	1 (1)	3 (3)
6. MS + AR	65 (6)	0	52 (80)	0	0	13 (20)
7. MR + AR	45 (4)	0	0	39 (87)	0	6 (13)
8. AS + MR	23 (2)	0	0	21 (91)	0	2 (9)
9. Tricuspid stenosis + MS ± AS	28 (3)	0	0	0	4 (14)	24 (86)
Totals	1,010 (100)‡	363 (36)	254 (25)	273 (27)	18 (2)	102 (10)

AV = aortic valve; MV = mitral valve; TV = tricuspid valve.

* Excludes patients with mitral regurgitation secondary to coronary heart disease (papillary muscle dysfunction), carcinoid heart disease, and hypertrophic cardiomyopathy and those with infective endocarditis limited to 1 or both right-sided cardiac valves. Tricuspid valve regurgitation was present in many patients in most of the 9 functional groups. All patients were in functional class III or IV (New York Heart Association), and more than half had 1 or more cardiac operations.

† In many patients, the aortic valve cusps actually were normal and the regurgitation was the result of disease of the aorta (Marfan and Marfan-like syndromes, syphilis, systemic hypertension, healed aortic dissection).

‡ The hearts in all 1,010 patients were examined and classified by WCR.

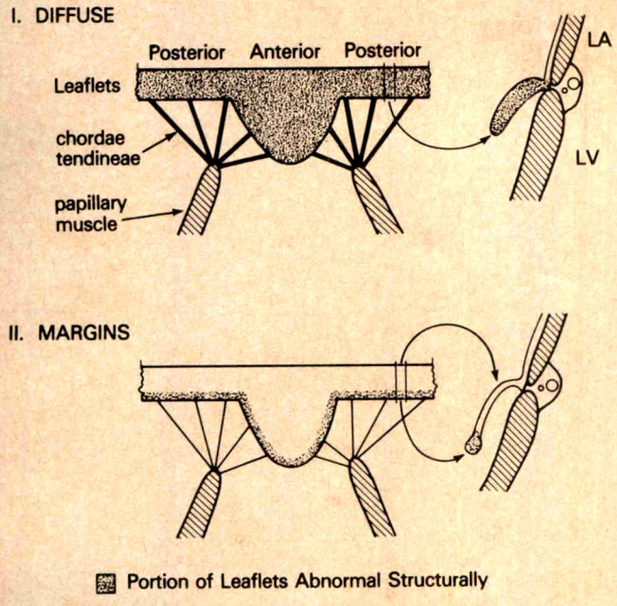

FIGURE 2. Diagram showing the 2 types of anatomic involvement of the mitral valve in rheumatic heart disease. Thickening of chordae are not required for diagnosis, only thickening of the leaflets, either diffusely or on all margins. LA = left atrium; LV = left ventricle. (Reprinted, by permission, from Roberts and Virmani.[11])

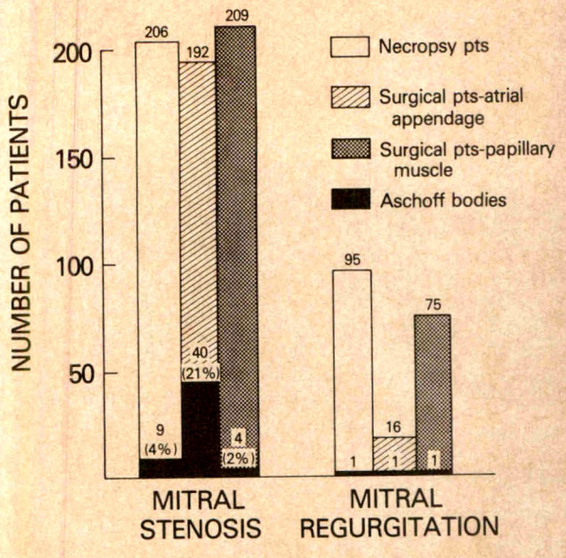

FIGURE 3. Bar graph demonstrating number and percentage of patients (pts) undergoing operations for either mitral stenosis (with or without mitral regurgitation) and pure mitral regurgitation in whom Aschoff bodies were found in either the left atrial appendage or left ventricular papillary muscle.

chordae are attached to leaflets as to papillary muscles. On an average, 24 chordae tendineae are attached to the papillary muscles (12 to each), and 120 chordae are attached to the leaflets.[3] The chordae insert onto the undersurfaces—that is, the ventricular surfaces—of both leaflets. The chordae subdivide as they progress from papillary muscle to leaflet. The subdivisions may be viewed as primary (first order), secondary (second order), and tertiary (third order) chordae. The spaces between the chordae serve as secondary orifices between left atrium and left ventricle. Obviously, the major orifice is the area between the leaflets, but much blood passes between the interchordal spaces. Therefore, fusion of chordae tendineae may narrow the mitral inlet.

The 2 *left ventricular papillary muscles* are preferably designated anterolateral and posteromedial.[3] There is considerable variation in the appearances of these 2 structures in the same person, and comparison of corresponding structures in different persons discloses considerable variation. The anterolateral papillary muscle is generally the more uniform of the 2. It usually consists of a single trunk that protrudes more into the cavity than does the posteromedial one. The posteromedial papillary muscle is generally smaller than the anterolateral structure and often consists of 2 or 3 smaller pillars rather than a single pillar. The posteromedial muscle usually has several connections to the left ventricular wall in addition to the base of the major trunk. Both papillary muscles are attached to the left ventricular free wall roughly at the junction of the caudal third and middle thirds.

With aging, the mitral valve, like other tissues, changes; this change consists mainly of focal fibrous thickening of both leaflets and chordae. The left ventricular cavity becomes smaller (presumably because the cardiac output decreases) as we grow older,[2,4] and consequently less area becomes available in the left ventricle to accommodate the mitral leaflets and chordae. The leaflets then contact one another abnormally during ventricular systole and focal fibrous thickening results. Since the left ventricular cavity diminishes with age, the mitral *anulus* does also. The latter change further increases the abnormal contact of the mitral leaflets with one other and furthers the leaflet scarring. This scarring from aging, however, is not enough to cause mitral dysfunction.

Abnormal Mitral Valve

Mitral Stenosis

The essential hemodynamic fault caused by mitral stenosis (MS) is the inability of the left atrium to empty normally.[2] In sinus rhythm, left atrial contraction serves to augment its emptying, but atrial contraction is lost in atrial fibrillation. The obstruction, represented by a pressure gradient across the valve, results in pulmonary venous obstruction which may be apparent on chest roentgenography.

Of the 9 single or combined cardiac valve lesions severe enough to be fatal, MS, in my experience, ranks second[5,6] (Table I). Of 1,010 patients >14 years of age with functionally severe (class III or IV, New York Heart Association) valvular cardiac disease whom I had studied at necropsy up to 1980, 434 (44%) had MS.[2] Only aortic valve stenosis was more common.[7–9] Mitral

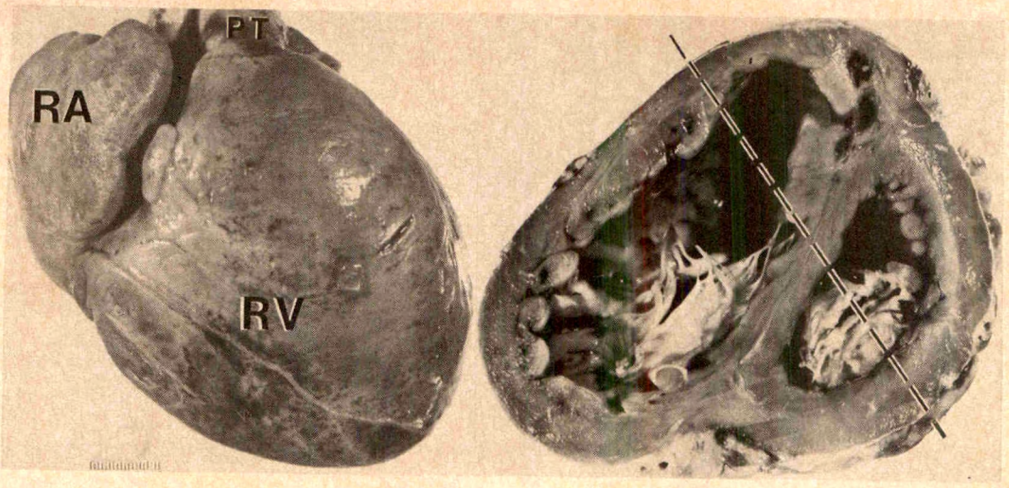

FIGURE 4. Heart in a 16-year-old boy (NIH #A77-232) who had acute rheumatic fever at age 6 years and chronic congestive heart failure beginning at age 10 years. By examination, the patient had evidence of severe mitral stenosis and tricuspid regurgitation. At cardiac catheterization 10 hours before death, the right ventricular pressure was 100/20 and the left ventricular pressure, 100/10 mm Hg. Neither pulmonary arterial wedge or left atrial pressures were obtained. Left ventriculogram disclosed no mitral regurgitation and a normal-sized left ventricular cavity. The patient had acute pulmonary edema after catheterization and underwent closed mitral commissurotomy as a terminal procedure on the ward. At necropsy, the heart weighed 450 g (the patient weighed 43 kg). The right atrium (RA) and ventricle (RV) were huge, and the thickness of the free walls of both ventricles were similar. Both mitral and tricuspid valve leaflets were diffusely thickened but free of calcific deposits. No Aschoff bodies were present. The **dashed straight line** is the line of the M-mode beam. PT = pulmonary trunk.

stenosis occurred alone in 189 (44%) patients and in combination with other functional valvular lesions in the other 245 (56%) patients. Mitral stenosis was rheumatic in origin in all 434 patients.[10,11]

Although a functional classification of valvular heart disease is most useful from physiologic and therapeutic standpoints, an anatomic classification is helpful from an etiologic standpoint. Five anatomic categories have proved useful: isolated mitral, isolated aortic, combined mitral and aortic, combined tricuspid and mitral with

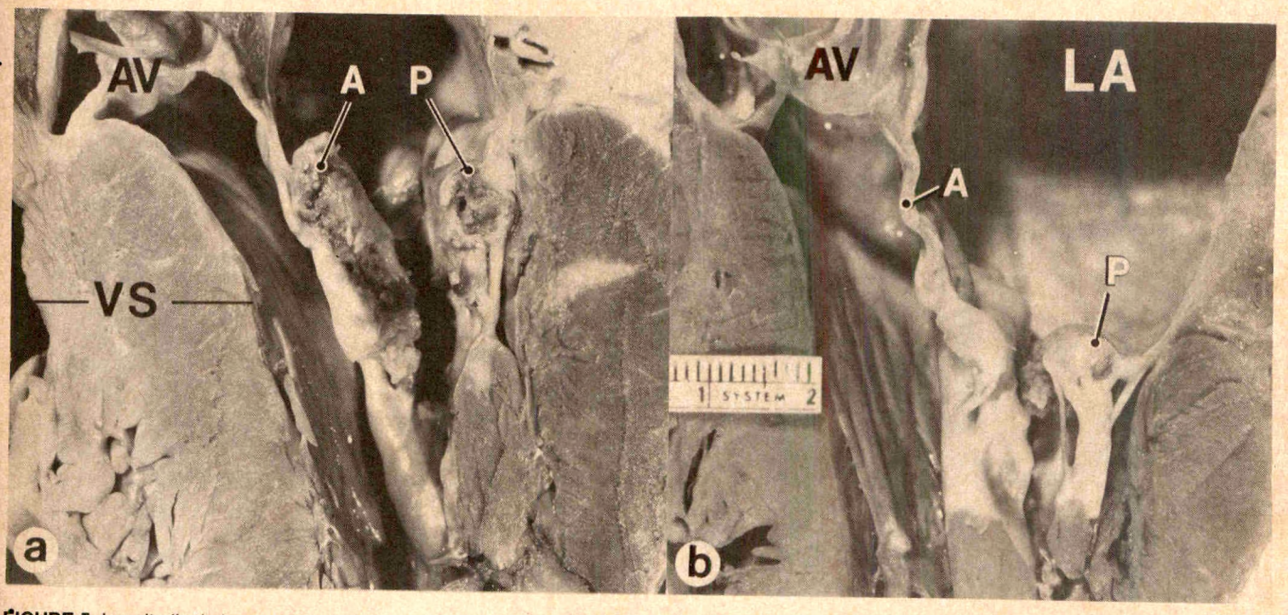

FIGURE 5. Longitudinal views, as would be seen by M-mode echocardiogram, of 2 hearts of patients with severe mitral stenosis. **a,** in a 55-year-old man (GT #74A-69) with equal peak systolic pressures in the right and left ventricles and no associated mitral regurgitation. The patient died from massive bleeding during cannulation of the aorta for planned mitral valve replacement. Both anterior (A) and posterior (P) mitral leaflets are heavily calcified. AV = aortic valve; VS = ventricular septum. **b,** in a 64-year-old woman (GT #78A-129) with right and left ventricular peak systolic pressures of 100 and 135 mm Hg, respectively, and an 18 mm Hg mean diastolic gradient between pulmonary arterial wedge position and left ventricle just before closed mitral commissurotomy 3 years before death. This patient died of progressive congestive cardiac failure. The heart weighed 410 g. The amount of calcium in the thickened mitral leaflets is relatively mild. LA = left atrium.

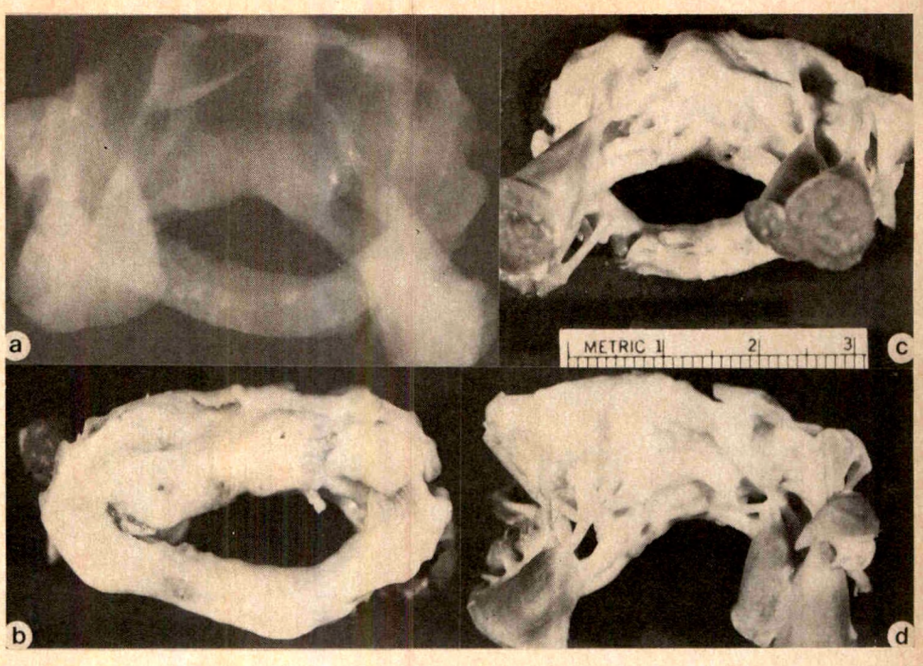

FIGURE 6. Operatively excised stenotic mitral valve in a 40-year-old woman with only a minute calcific deposit in the anterior leaflet. The mean diastolic gradient between the pulmonary arterial wedge position and the left ventricle was 13 mm Hg, the peak pulmonary arterial systolic pressure was 50 mm Hg, and 3+/4+ mitral regurgitation was present by left ventriculogram. **a,** radiogram of operatively excised valve. **b,** view from left atrial aspect. **c,** view from left ventricular aspect. **d,** view of anterior leaflet and papillary muscles. (Reprinted, by permission, from Lachman and Roberts.[18])

or without aortic, and both tricuspid and mitral (Table I). Anatomically isolated aortic valve disease is never rheumatic in origin.[5] Isolated mitral disease causing MS is, with rare exception, rheumatic in origin, but isolated mitral disease causing pure regurgitation is usually nonrheumatic in origin.[12] Anatomic valve disease involving more than 1 cardiac valve is usually rheumatic in origin. Isolated anatomic disease of the tricuspid or pulmonic valves, or both, is usually congenital or infectious in origin or is associated with the carcinoid syndrome.[13–17]

A valve may function normally and yet be anatomically abnormal. Only 62% of the 189 patients with isolated MS (with or without mitral regurgitation [MR]) had anatomic involvement limited to the mitral valve[6] (Table I). In contrast, 88% of the 292 patients with clinically isolated aortic valve stenosis (with or without regurgitation) had anatomic disease limited to the aortic valve only.

Rheumatic heart disease may be viewed as a disease of the mitral valve; other valves also may be involved both anatomically and functionally, but anatomically the mitral valve is always involved[11] (Fig. 2). To my knowledge, *Aschoff bodies* have never been found in hearts without anatomic disease of the mitral valve.[11] Of the first 543 patients with severe valvular heart disease whom I studied at necropsy, 11 (27%) had Aschoff bodies, and all had anatomic mitral valve disease. The ages of the 11 patients with Aschoff bodies ranged from 18 to 68 years (mean 38) and 9 had a history of acute rheumatic fever earlier in life. Clinical study revealed that 9 of the 11 patients had MS with or without dysfunction of 1 or more other cardiac valves, 1 had isolated pure aortic regurgitation, and 1 had both mitral and aortic regurgitation. All 11 patients had diffuse fibrous thickening of the mitral valve leaflets and all but 1 had diffuse anatomic lesions of at least 2 other cardiac valves. No patient with anatomic lesions limited to the aortic valve had Aschoff bodies. Thus, among patients with chronic valvular heart disease, Aschoff bodies, the only anatomic lesion pathognomonic of rheumatic heart disease, usually indicate diffuse anatomic lesions of 1 or more other cardiac valves. The functional mitral lesion is usually stenosis.

Although they are rare at necropsy in patients with fatal chronic valvular heart disease, Aschoff bodies are fairly common in the heart in patients having mitral valve commissurotomy for MS.[10] Among 481 patients undergoing various mitral valve operations, Aschoff bodies were found in 40 (21%) of 191 operatively excised left atrial appendages, in 4 (2%) of 273 operatively excised left ventricular papillary muscles (1 per patient), and in 1 (6%) of 17 patients with both left atrial appendage and papillary muscle operatively excised (Fig. 3). Of the 45 patients with Aschoff bodies, 44 had MS preoperatively, and only 1, a 10-year-old boy, had pure MR. Sinus rhythm was present in 38 (84%), and atrial fibrillation in 7 (16%). Perioperatively, only 1 of the 45 patients with Aschoff bodies had clinical or laboratory stigmata compatible with acute rheumatic fever, and 58% had an illness compatible with acute rheumatic fever at any time.

Rheumatic heart disease not only is a disorder of the cardiac valves; it also affects mural endocardium, pericardium, and myocardium. On histologic study, the atrial walls virtually always have increased amounts of fibrous tissue in both myocardial interstitium and in the mural endocardium, atrophy of some and hypertrophy of other myocardial cells, and hypertrophy of smooth muscle cells of the mural endocardium. In all patients with rheumatic MS, the leaflets are diffusely thickened, either by fibrous tissue or calcific deposits or both; the

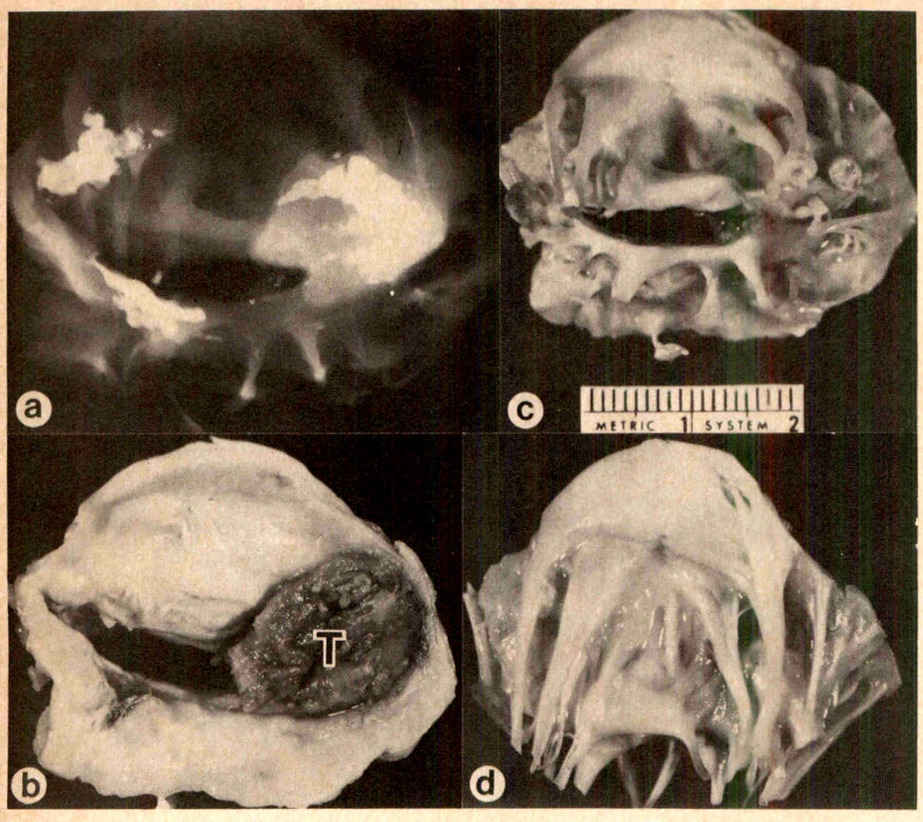

FIGURE 7. Operatively excised stenotic mitral valve in a 72-year-old woman (S76-76) who had had an embolus to a femoral artery 5 years earlier. **a,** radiogram of the operatively excised valve showing focal calcific deposits. **b,** view of the valve from the left atrial aspect showing an oval thrombus (T) over half of the orifice. No thrombus was present in the left atrial cavity. **c,** view of the valve from the left ventricular aspect. The orifice is eccentric. **d,** view of the anterior leaflet.

commissures are usually fused, and the chordae tendineae are shortened and usually fused to some degree (Fig. 4 to 8). The great obstruction to this funnel-shaped valve occurs at its apex, which is within the left ventricular cavity. The primary orifice, located at the level of the anulus, is far less narrowed. Fusion may involve 1 or both commissures. When only 1 is fused or 1 is fused more than the other, the stenotic orifice is eccentrically located. A centrally located orifice indicates symmetrical commissural fusion. In rheumatic MS, the chordae tendineae are occasionally so retracted that the leaflets appear to insert directly into the papillary muscles. When this occurs, the MS is always severe because the interchordal spaces are almost entirely obliterated. Sometimes chordae inserting into 1 papillary muscle are well preserved, whereas those inserting into the other papillary muscle are partially or completely fused. Mitral commissurotomy on a valve in which the leaflets insert almost directly into the papillary muscle(s) usually must include a splitting of the papillary muscle(s) as well as the commissure(s). If there are normally about 120 third-order chordae and about 24 first-order chordae, in MS these numbers are usually halved and, on occasion, even reduced to just 1.

The amount of *calcium* in the leaflets of stenotic mitral valves varies considerably[18] (Figs. 6 to 8). Generally, calcium is more frequent and in larger quantity in men than in women, in older than in younger patients, and in patients with higher compared with those with lower pressure gradients between left atrium and left ventricle[18] (Fig. 9). The rapidity with which calcium develops also varies considerably; it is present at a younger age in men than in women.[18] Lachman and I[18] determined the presence or absence and the extent of calcific deposits in operatively excised stenotic mitral valves by radiography of the excised valve in 164 patients aged 26 to 72 years. The extent of the mitral calcific deposits was determined by the percentage of the valvular circumference containing the deposits: grade 0 (14 patients); grade I = 1 to 25% (43 patients); grade II = 26 to 50% (34 patients); grade III = 51 to 75% (39 patients); and grade IV = 76 to 100% (34 patients). The amount of calcific deposits in the stenotic mitral valves correlated with *sex* and with the *mean diastolic pressure gradient across the mitral valve* ($p < 0.05$) (Fig. 9), but it did not correlate with the patient's age (after age 25 years), cardiac rhythm, pulmonary arterial or pulmonary arterial wedge pressure, previous mitral commissurotomy, presence of thrombus in the body of left atrium, or the presence of disease of 1 or more other cardiac valves.

Among the 164 patients with MS having mitral valve replacement and roentgenography of the excised mitral valve, 14 had no mitral calcium and 43 had only trace or minimal mitral calcific deposits. Thus, we[19] wondered why these 57 patients had mitral replacement rather than mitral commissurotomy. Of the 57 patients, 37 had moderate to severe MR and, therefore, clearly deserved mitral valve replacement. The remaining 20 had absent or minimal calcific deposits, but, nevertheless, they too

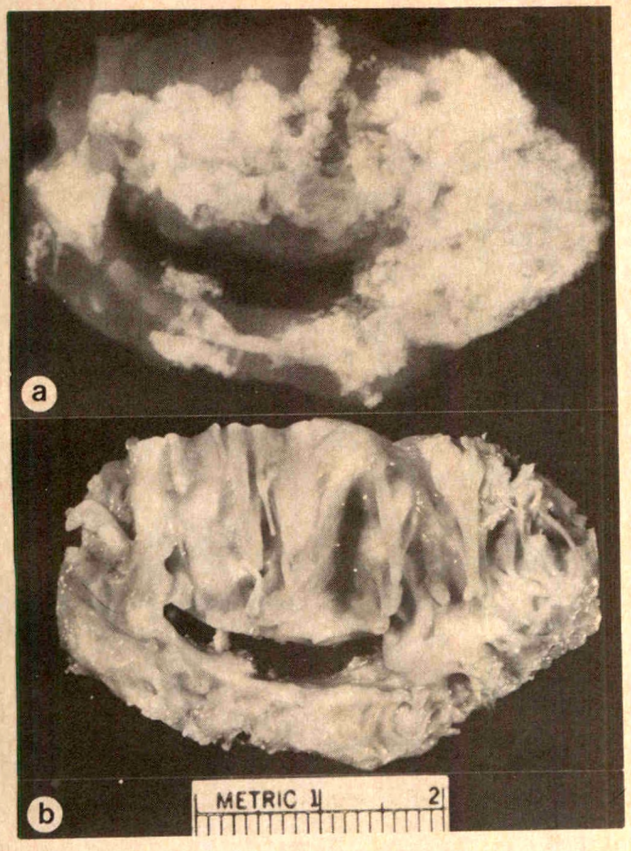

FIGURE 8. Operatively excised stenotic heavily calcified mitral valve in a 53-year-old woman (S67-867) in whom the mean diastolic gradient between the pulmonary arterial wedge position and the left ventricle was 26 mm Hg. She also had 1+/4+ mitral regurgitation by left ventriculogram; a thrombus was present in the body of left atrium. **a,** radiogram of the operatively excised valve. **b,** view of the valve from the left ventricle after excision of the papillary muscle. The orifice is eccentric. (Reprinted, by permission, from Lachman and Roberts.[18])

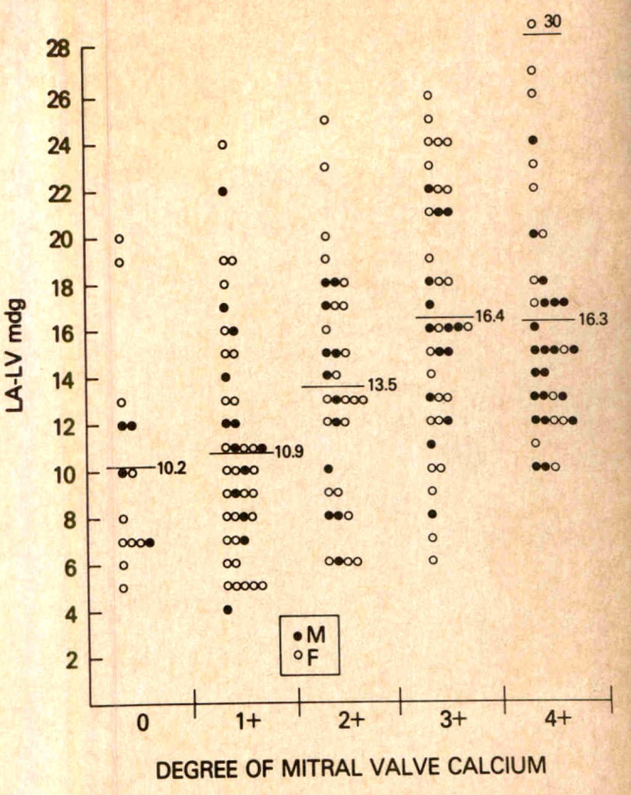

FIGURE 9. Relation between the left atrial (LA) left ventricular (LV) mean diastolic gradient (mdg) and degree of mitral valve calcium. (Reprinted, by permission, from Lachman and Roberts.[18])

had mitral valve replacement. Although in the prevalve replacement era all 20 patients almost surely would have been considered good or ideal candidates for mitral commissurotomy, other factors swung the surgeon to valve replacement rather than commissurotomy. These factors included the need to replace 1 or more other cardiac valves (13 patients), the utilization of cardiopulmonary bypass allowing visual inspection rather than simple palpation of the diseased mitral valve (all 20 patients), relatively little experience with mitral commissurotomy in 4 of the 5 surgeons (17 patients), displeasure with attempted commissurotomy (3 patients), previous mitral commissurotomy (11 patients), and incorrect identification of mitral calcific deposits (2 patients). Even though mitral commissurotomy has been in use for 30 years, the mere alternative of valve replacement may have altered the definition of the stenotic mitral valve previously considered ideal for mitral commissurotomy.

A major complication of MS is *thrombus formation in the left atrial cavity.* The thrombus may be limited to atrial appendage (most common) or be located in both left atrial appendage and body (Fig. 10). The latter group hereafter will be referred to as "left atrial body thrombus." Left atrial body thrombus was observed in 5% of 1,010 personally studied necropsy patients with fatal valvular heart disease; all had severe MS (Table I). Left atrial body thrombus was not observed in any of the 165 patients with pure MR with or without aortic valve dysfunction. All patients with left atrial body thrombi had atrial fibrillation. Comparison of these necropsy patients with 46 patients with MS operated upon at the National Heart, Lung, and Blood Institute and in whom thrombus was found at operation in the left atrial body disclosed that 42 (91%) patients had atrial fibrillation. In contrast, of 40 living patients undergoing mitral valve replacement for pure MR and operated upon at the National Heart, Lung, and Blood Institute, none had thrombus in the body of the left atrium, although 75% had atrial fibrillation. *Thrombus appears to occur in the body of the left atrium only in patients with MS, and atrial fibrillation without MS is incapable of forming a thrombus in the left atrial body.*

Calcific deposits on the mural endocardium of the left atrium are indicative of previous organization with calcification of left atrial thrombi. Histologically, the "calcific thrombi" also contain cholesterol clefts and are identical to atherosclerotic plaques. The observation that left atrial thrombi can organize into lesions iden-

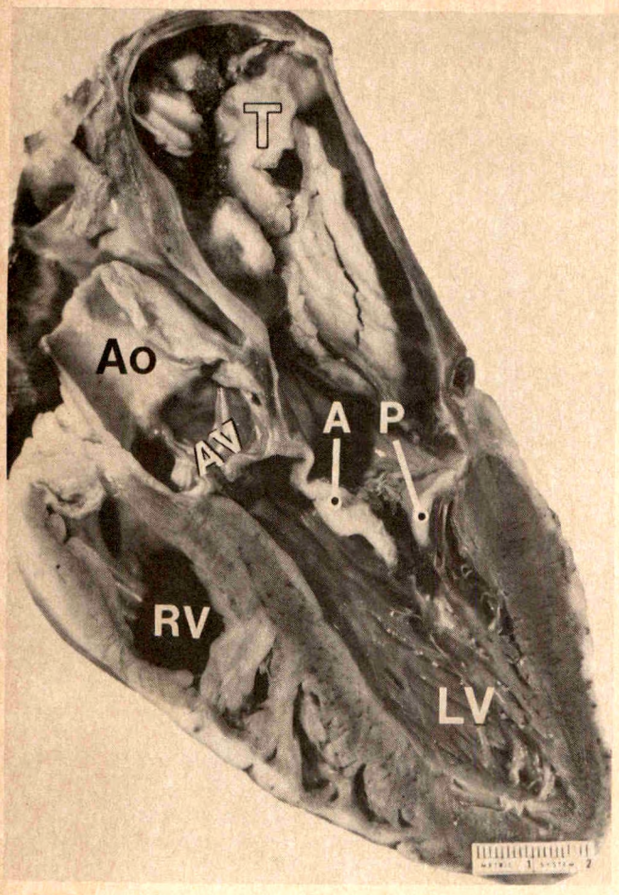

FIGURE 10. Long-axis view of the heart in a 53-year-old woman (GT#77A-190) in whom a huge thrombus (T) was found in the body of the left atrium at necropsy. The mitral valve is quite stenotic. The aortic valve (AV) is normal. A = anterior and P = posterior mitral leaflet; Ao = aorta; LV = left ventricle; RV = right ventricle. Mitral valve commissurotomy had been recommended when the patient was 40 years of age, but she declined. Her last 2 years were characterized by chronic progressive congestive cardiac failure complicated by anemia from multiple myeloma. The patient had chronic atrial fibrillation, but never had cardiac catheterization, a cardiac operation, or evidence of systemic emboli.

tical to atherosclerotic plaques supports the view that atherosclerotic plaques may be the result of organization of thrombi. If calcific deposits form on left atrial body endocardium before the left atrial cavity has had time to dilate, this cavity may be prevented thereafter from dilating. The elevated left atrial pressure may lead more rapidly to pulmonary venous, pulmonary arterial, and right ventricular dilatation with subsequent tricuspsid regurgitation and development of huge right atrial dilatation.[20]

Nonrheumatic causes of MS include *congenital anomalies*[21] (Fig. 11); *neoplasms* (Fig. 12) (particularly myxoma[22]) protruding through the mitral orifice from the left atrium (but malignant neoplasms primary or secondary in the lung may grow into the mitral orifice by way of the pulmonary veins[23]); *large vegetations from active infective endocarditis*[24,25]; and *massive mitral anular calcific deposits*, particularly when associated with small-sized left ventricular cavities and left ventricular outflow tract obstruction[26] (Fig. 13). A relatively new, acquired cause of MS is a *mechanical prosthetic or bioprosthetic cardiac valve.*[27–29] Since the native mitral valve is within the left ventricle, a prosthetic mitral valve also is located within this cavity. The prosthesis must be small enough for the contracting left ventricular wall not to interfere with movement of the prosthetic poppet or disk. When the prosthesis is too large for the cavity into which it was inserted, the poppet may be prevented from moving adequately and may therefore obstruct left atrial emptying. The latter state is far more common than obstruction to left ventricular emptying by the prosthesis. Thrombus formation on a mitral prosthesis also may obstruct left atrial emptying.

Pure Mitral Regurgitation

In contrast to MS, which has mainly 1 cause (rheumatic), pure MR has numerous causes.[2,3,12,16,17,23,30–60] Of the 1,010 patients with functionally severe valvular heart disease, excluding papillary muscle dysfunction, studied personally at necropsy, 165 (16%) had pure (no element of stenosis) MR[5] (Table I); the MR was isolated in 97 of these patients (59%) and associated with aortic valve dysfunction in 68 (41%) (aortic regurgitation in 45 and aortic stenosis in 23). In the 68 patients with associated aortic valve dysfunction, the origin of the valvular disease was rheumatic. Of the 97 patients with clinically isolated pure MR, the aortic valve or the tricuspid valve or both was anatomically abnormal (mild diffuse scarring) in 12 and therefore the cause of the mitral valve dysfunction in these patients was also rheumatic in origin (Table I). Of the remaining 85 patients, the origin of the pure MR was usually nonrheumatic, most commonly ruptured chordae tendineae from infection on a previously normal valve or spontaneous rupture with underlying prolapsing (or floppy) mitral leaflet(s).

Why the mitral valve affected by acute rheumatic fever becomes stenotic in some patients and purely regurgitant in others (mainly children) is unknown. Although the cause may be similar (rheumatic), the structural alterations in the purely regurgitant mitral valve are quite different from those in the stenotic valve. The purely regurgitant rheumatic valve infrequently contains calcific deposits, its commissures are virtually never fused, and its chordae tendineae are only mildly thickened, if at all; chordal fusion is infrequent (Fig. 14). It is often difficult to explain adequately the mechanism of MR in a valve made purely regurgitant by consequences of rheumatic fever. The mitral anuli in children with rheumatic MR usually are dilated but this mechanism is most often not applicable in adults with rheumatic MR.

Rheumatic disease is never limited to endocardium. Inflammatory cells are nearly always found in atrial walls of patients dying with acute rheumatic fever.[61] The inflammation appears to weaken the walls, and superimposed MR tends to dilate the chamber out of proportion to the dilation that would occur with similar degrees of MR into a left atrium with previously normal

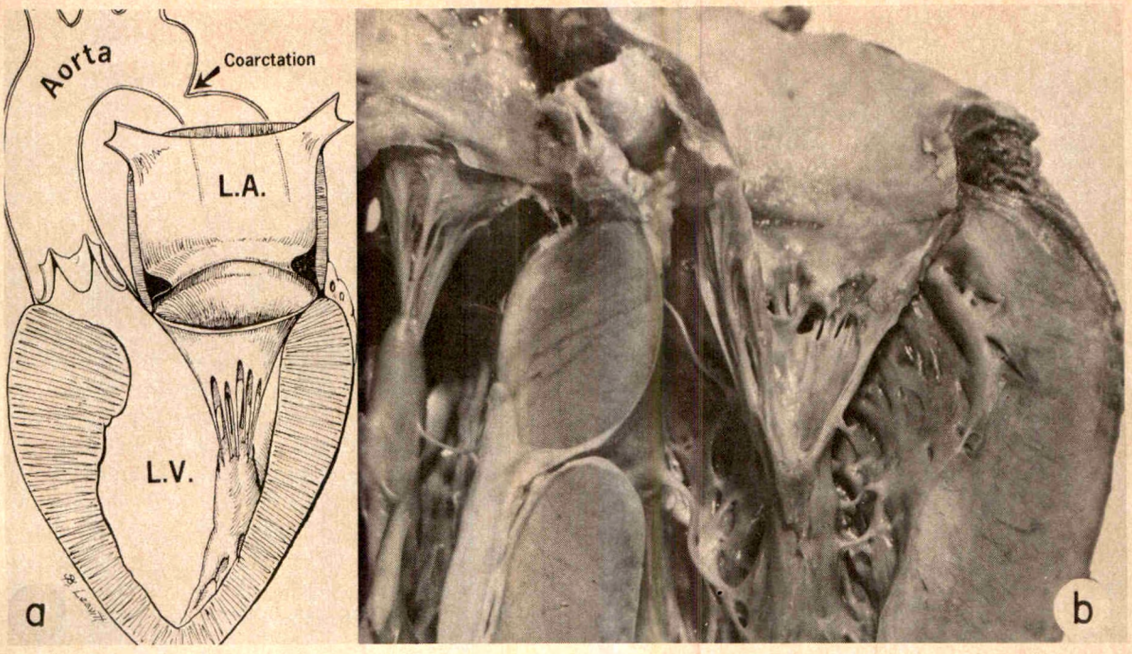

FIGURE 11. Parachute mitral valve causing mitral stenosis in a 14-year-old boy (GT #71A-215) who presented clinically with signs of left ventricular outflow obstruction. The peak systolic gradient between the left ventricle (L.V.) and a systemic artery was 80 mm Hg. Obstruction was caused by a small aortic "anulus" with a bicuspid aortic valve and by discrete obstruction just below the aortic valve. At necropsy, the mitral valve showed a parachute configuration, and all of its chordae inserted into a single left ventricular papillary muscle. Preoperatively, the left atrial mean pressure was 30 mm Hg, and the pulmonary arterial systolic pressure was 50 mm Hg. It was not realized while the patient was alive, however, that the mitral valve was stenotic. In addition, a functionally insignificant coarctation of the aorta was present. A ventricular septal defect had closed spontaneously. L.A. = left atrium. (Reprinted, by permission, from Roberts and Cohen.[3])

walls.[41] What causes the left atrium to dilate enormously in some patients with rheumatic MR is uncertain. Possibly, the patients with so-called giant atria have had more frequent or more severe attacks of acute rheumatic fever, with particularly severe destruction of atrial myocardial fibers. When the left atrium in pure MR is giant in size (Fig. 15), intimal proliferation is rarely found in the pulmonary veins or arteries, and the right ventricular walls are not hypertrophied.[41,47] The larger the left atrial cavity in pure MR, the lower its intracavity pressure. Since the right ventricular walls in these patients are usually not hypertrophied (because the right ventricular systolic pressures are normal or near normal), tricuspid regurgitation is infrequent. In contrast, patients with large left atria from MS or from combined MS and MR have elevated left atrial, pulmonary venous, pulmonary arterial, and right ventricular pressures; the right ventricular walls therefore are

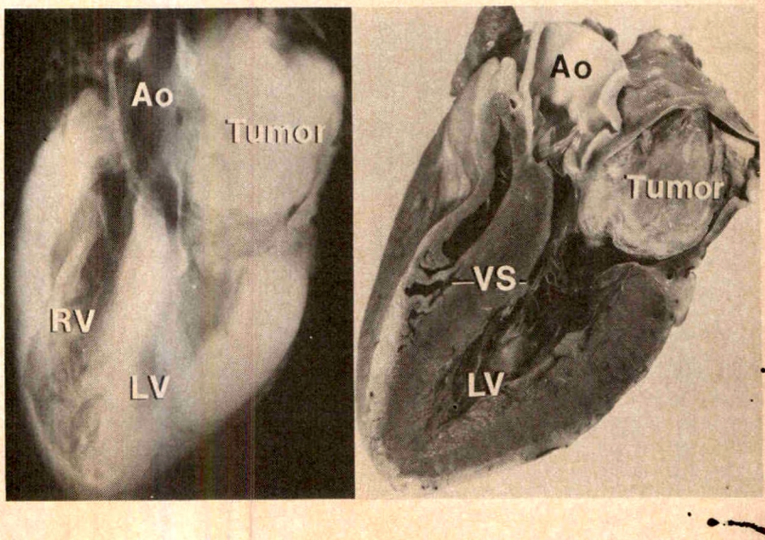

FIGURE 12. Metastatic ovarian carcinoma to the lung with extension into the pulmonary veins and from there into the left atrial body to partly obstruct the mitral orifice in a 44-year-old woman (NNMC #A76-150) who had been asymptomatic until 6 weeks before death, when evidence of congestive heart failure appeared. A precordial murmur was not recorded. **a,** radiogram of heart at necropsy showing a mass in the left atrium and **b,** a long-axis view of heart. Ao = aorta; LV = left ventricle; RV = right ventricle; VS = ventricular septum.

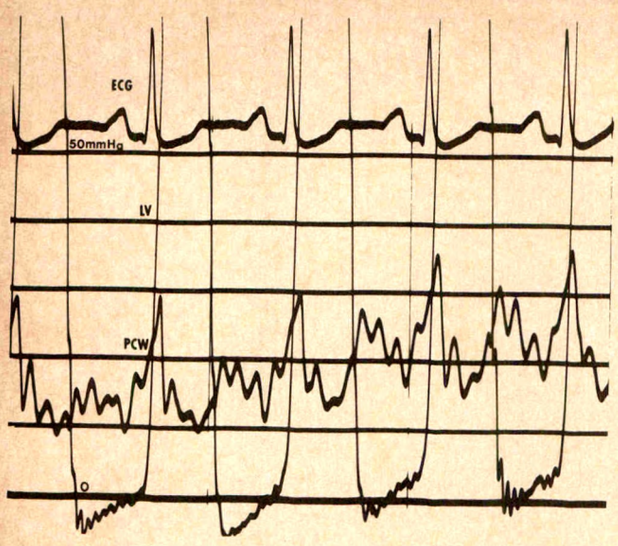

FIGURE 13. Simultaneous, equisensitive recording of pulmonary arterial wedge (PCW) and left ventricular (LV) pressures in a 70-year-old woman (GT #74A-287) with severe (153 mm Hg peak systolic gradient) aortic valve stenosis and massive (4+/4+) mitral anular calcium producing a 15 mm Hg mean diastolic pressure gradient at the level of the otherwise anatomically normal mitral valve. Thus, heavy mitral anular calcific deposits in the setting of left ventricular outflow obstruction can produce "mitral stenosis." ECG = electrocardiogram. (Reprinted, by permission, from Hammer et al.[26])

hypertrophied. Thus, tricuspid regurgitation is a common consequence.

Rupture of mitral chordae tendineae is another common cause of fatal or potentially fatal pure MR.[41,42] The normal chordae tendineae are the ones most likely to rupture, not the previously thickened ones. Thus, rupture of 1 or several thick chordae tendineae in patients with MS is extremely rare. The cause of the rupture varies. Infective endocarditis is the most common cause of acute rupture[41] (Fig. 16). Of 42 patients with healed ruptured mitral chordae tendineae studied by Buchbinder and me, however, only 14 had had infective endocarditis. Infective endocarditis causes acute severe MR by chordal rupture and rarely by leaflet perforation[16] (Fig. 17). The syndrome of acute severe MR associated with normal- or near-normal–sized left atria and severe elevations of left atrial, pulmonary venous, pulmonary arterial, and right ventricular pressures is usually the result of rupture of chordae tendineae by infective endocarditis involving previously normal valves[41] (Fig. 18). The left atrial myocardial fibers in these patients, as contrasted to those in patients with chronic rheumatic MR, have not been previously damaged by rheumatic fever, and, therefore, the left atrial wall is capable of responding to the sudden elevation of left atrial pressure by vigorous contractions, leading to myofiber hypertrophy. The ventricular sys-

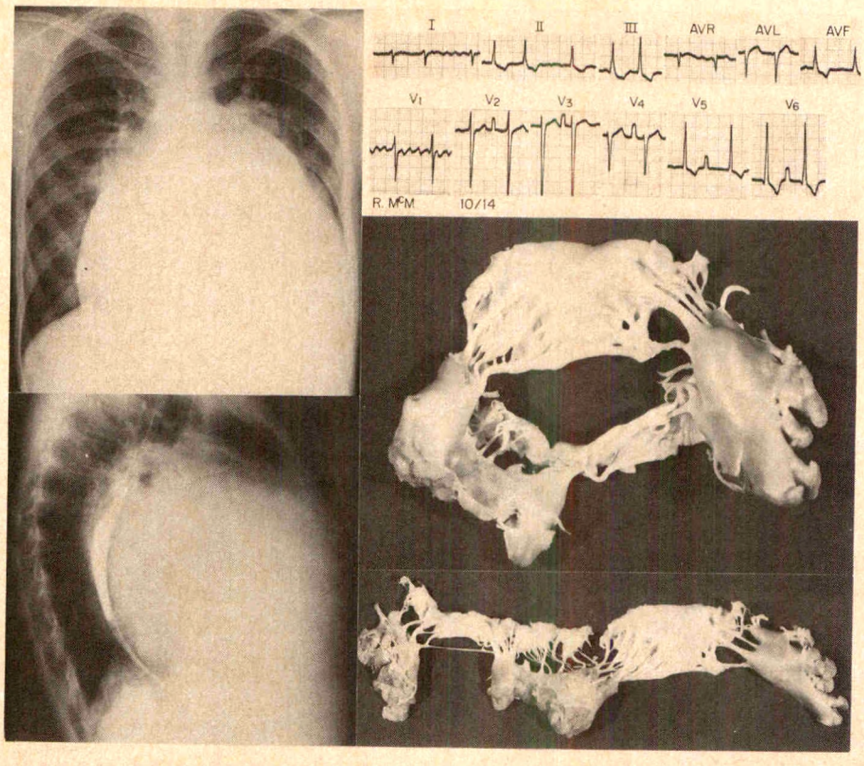

FIGURE 14. Pure mitral and tricuspid valve regurgitation of rheumatic origin in a 15-year-old girl (A63-230) who died 2 days after mitral valve replacement. Shown are posteroanterior and lateral radiograms and an electrocardiogram immediately preoperatively and the intact and opened operatively excised mitral valve. The patient had acute rheumatic fever at ages 6 and 8 years and a prominent "malar flush." The right ventricular and femoral arterial peak systolic pressures were 70 and 110 mm Hg, respectively, preoperatively. The mitral leaflets are diffusely thickened but only mildly so. No Aschoff bodies were present.

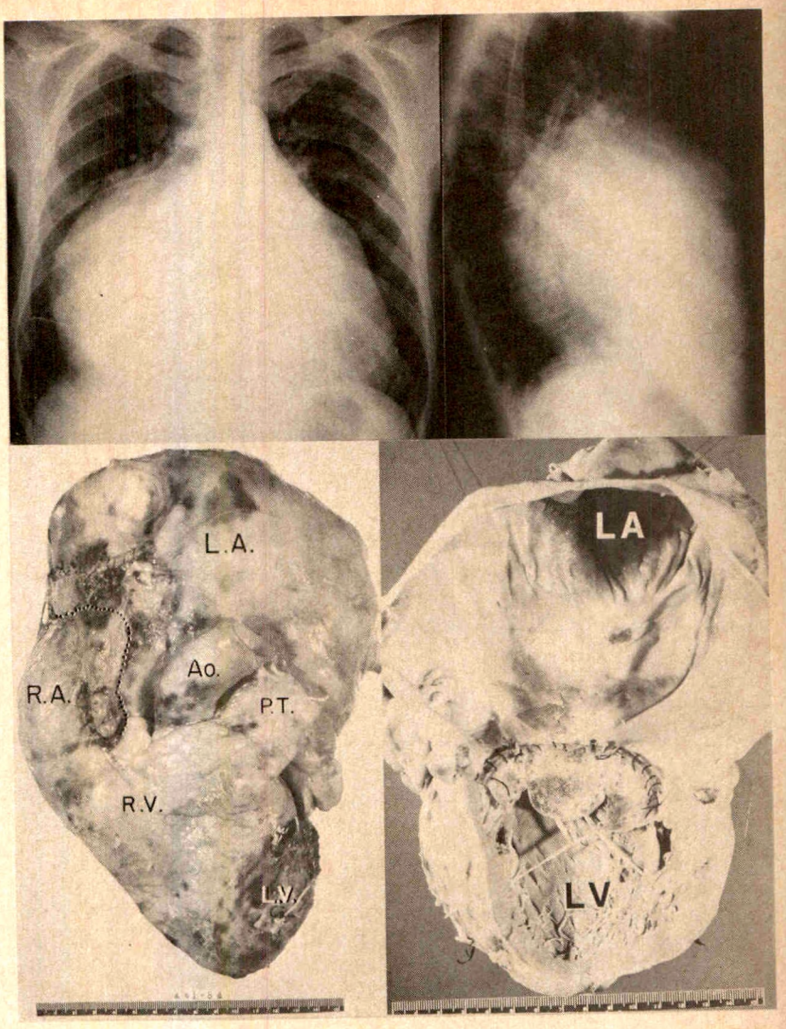

FIGURE 15. Giant-sized left atrium (LA) in a 49-year-old man (A61-84) with severe mitral regurgitation combined with mitral stenosis of rheumatic origin. The right and left ventricular peak systolic pressures were 30 and 100 mm Hg, respectively. The left atrium was entered by a needle inserted into the right mid-axillary line. The patient died 6 hours after mitral replacement. **Lower left,** the giant-sized left atrium is apparent. The **dotted line** outlines the right atrium (RA). Ao = aorta; LV = left ventricle; PT = pulmonary trunk; RV = right ventricle. **Lower right,** opened left atrium, mitral valve, and left ventricle (LV). The ruler units are in centimeters.

tolic pressures in these patients are reflected quickly into the vasculature of the lungs, and severe medial and intimal thickening of the pulmonary arteries and veins progress rapidly. The already diseased left atrium, in contrast, appears to respond to volume load by dilating, not by contracting. Thus, the smaller the left atrial cavity in pure MR, the thicker the right ventricular wall, and, conversely, the larger the left atrial cavity, the thinner the right ventricular wall[41] (Fig. 18).

A relatively new cause of acquired pure MR is *fistulas around the bases of prosthetic and bioprosthetic valves.*[29] Small peribasilar leaks around mitral prostheses are difficult to diagnose clinically without injecting contrast material into the left ventricle.

Although for years rheumatic heart disease has been considered the major cause of significant MR, most patients with rheumatic heart disease and MR also have some degree of MS as well. Of patients with *isolated* (aortic valve function normal), *pure* (no element of stenosis) MR severe enough to warrant mitral valve replacement, *mitral valve prolapse* is now recognized as the most common etiology (Fig. 19 to 22). My associates and I[12] recently reviewed the records and operatively excised mitral valves of 97 patients aged 32 to 78 years (mean 54) (57 men), who underwent mitral valve replacement because of $3^+/4^+$ or $4^+/4^+$ MR as determined by left ventricular angiography. Of the 97 patients, the cause of the MR was leaflet prolapse in 60 (62%), papillary muscle dysfunction from coronary heart disease in 29 (30%), infective endocarditis involving apparently previously normal mitral valve in 5 patients, and rheumatic heart disease in 3 patients (Fig. 23). Of the 60 patients with mitral prolapse, 13 had ruptured chordae tendineae and all 5 patients with infective endocarditis had ruptured chordae.

The circumference of the mitral anuli in the patients with prolapsed valves without ruptured chordae was significantly larger than those in the patients in other groups and in 18 control subjects, both of which were normal (Fig. 24 and 25). Likewise, the areas of the excised leaflets in the prolapsed valves were much larger than in the other groups and in the control subjects, both of which were normal (Fig. 26). The product of the circumference (in centimeters) multiplied by the area (in centimeters squared) calculated for the normal valves ranged from 45 to 140 cm^3 (average 91). The av-

erage product was 150 cm^3 in the prolapsed valves with ruptured chordae, and 273 cm^3 in the prolapsed valves with intact chordae. The products were 87, 93, and 106 cm^3, respectively, in the valves regurgitant because of papillary muscle dysfunction, infective endocarditis, or rheumatic disease; these products did not differ from those of the normal valves.

The correct cause of the MR in the 97 patients was usually predictable from the history alone. Of the 29 patients with papillary muscle dysfunction from atherosclerotic coronary heart disease, all had clinical evidence of myocardial ischemia: history of acute myocardial infarction which had healed in 24, a left ventricular aneurysm from a silent infarction in 1, and angina pectoris in 4. Of the 5 patients with MR secondary to infective endocarditis, 4 had well-documented episodes of infection that had been cured by antibiotic therapy; none had evidence of valvular dysfunction before the episode of infective endocarditis. Of the 3 patients with MR secondary to a rheumatic origin, 2 had a history of acute rheumatic fever, whereas this item was positive in only 5 of the other 94 patients. Clinical diagnosis of mitral valve prolapse was by a process of exclusion. Only 2 (3%) of the 60 patients had historical evidence of previous acute myocardial infarction; 5 (8%) had a history of acute rheumatic fever and 4 (7%) had a history of active infective endocarditis. Compared with the 5 patients classified as having ruptured chordae tendineae on previously normal valves (4 of whom had a history of infective endocarditis), the 4 patients with healed infective endocarditis and mitral prolapse were older (mean age 61 years versus 42 years), had previous systolic murmurs of MR before the episode of infective endocarditis (4 of 4 versus 0 of 5), and had a longer mean duration of congestive heart failure (11 months versus 4 months). Thus, of the 60 patients with prolapse, 51 (85%) had no historical evidence of myocardial ischemia, acute rheumatic fever, or infective endocarditis.

The origin of the MR also was suggested preoperatively by more objective means. All 29 patients with MR secondary to coronary disease had abnormal Q waves by electrocardiogram, whereas abnormal Q waves were present in only 4 of the 60 patients with mitral prolapse and in none of the 8 patients with MR from either in-

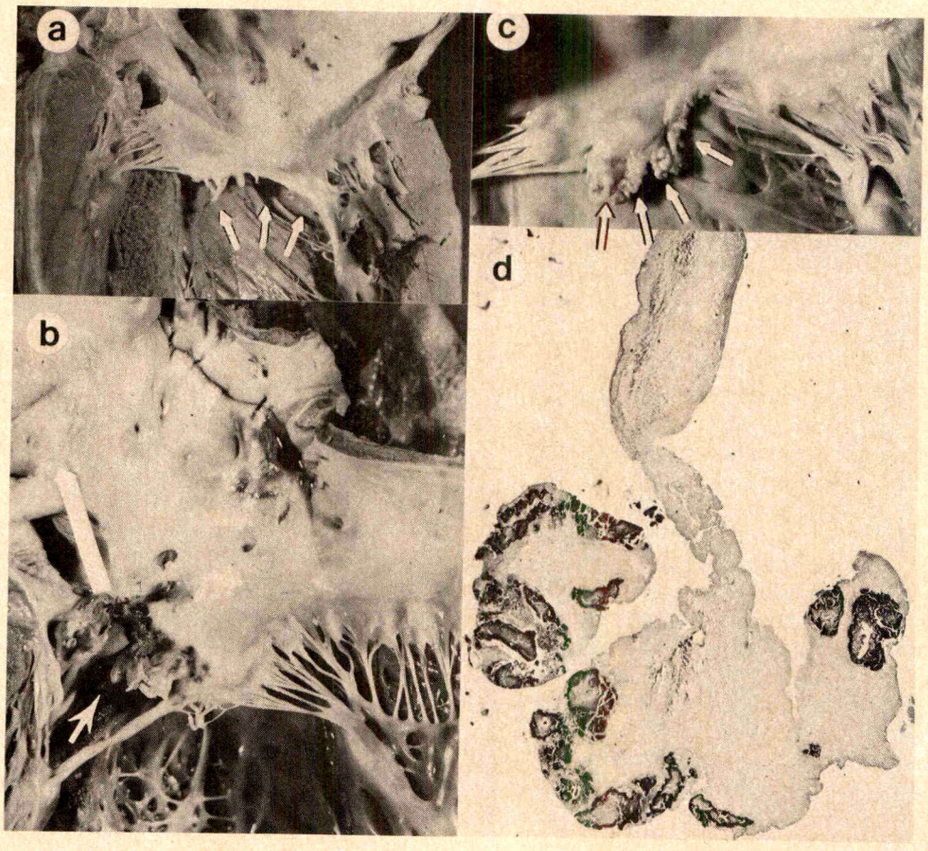

FIGURE 16. Ruptured mitral chordae tendineae (**short arrows**) in 3 patients: **a,** in a 29-year-old woman (A63-97) who had had Staphylococcus epidermidis endocarditis 5 years earlier on what appears to have been a previously anatomically normal valve. The peak systolic pulmonary arterial pressure was 105 mm Hg and the left atrial V wave, 35 mm Hg. **b,** in a 19-year-old girl (A61-221) who had had Streptococcus group D endocarditis 16 months earlier. The peak systolic pulmonary arterial pressure was 70 mm Hg and the left atrial V wave, 36 mm Hg. **c** and **d,** in a 24-year-old woman (A62-19) who had had enterococcus endocarditis 5 months earlier. The peak systolic pulmonary arterial pressure was 72 mm Hg and the left atrial V wave, 66 mm Hg. **d,** histologic section of mitral leaflet at site of chordal rupture showing calcific deposits. Hematoxylin and eosin stain. (Reprinted, by permission, from Roberts et al.[41])

fective endocarditis or rheumatic disease. Atrial fibrillation was significantly ($p < 0.05$) more common in the patients in whom the MR resulted from coronary disease: in 7 (24%) of these 29 patients, in only 4 (7%) of the 60 patients with mitral prolapse, and in 2 of the 8 patients with either infective endocarditis or a rheumatic origin. Of the 60 patients with prolapse, 43 had M-mode echocardiograms; in 32 (74%) prolapse was demonstrated. Of the 29 patients with coronary heart disease, M-mode echocardiograms were done in 22; only 2 (9%) demonstrated prolapse. Of the 8 patients with MR from infective endocarditis or rheumatic etiologies, 7 had

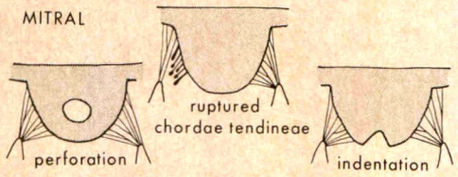

FIGURE 17. Types of mitral valve damage resulting from infective endocarditis.

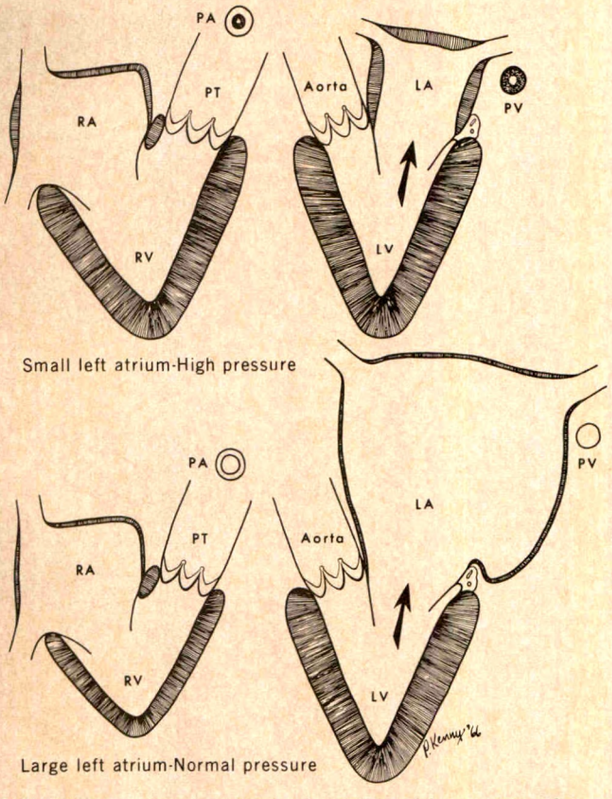

FIGURE 18. Diagram depicting the 2 extremes of the spectrum of pure mitral regurgitation. When severe mitral regurgitation appears suddenly in individuals with previously normal or near-normal hearts, the left atrium (LA) is relatively small and the high pressure within it is reflected back into the pulmonary vessels and right ventricle (RV). The anatomic indicator of this latter physiologic event is severe hypertrophy of the left atrial and right ventricular walls and marked intimal and medial thickening of the pulmonary arteries (PA), arterioles, and veins (PV). In the other extreme, the left atrial cavity is of giant size and its wall is thin. It is thus able to "absorb" the left ventricular (LV) pressure without reflecting it back into the pulmonary vessels or right ventricle. As a consequence, the pulmonary vessels remain normal and the right ventricular wall does not thicken. PT = pulmonary trunk; RA = right atrium. (Reprinted, by permission, from Roberts et al.[47])

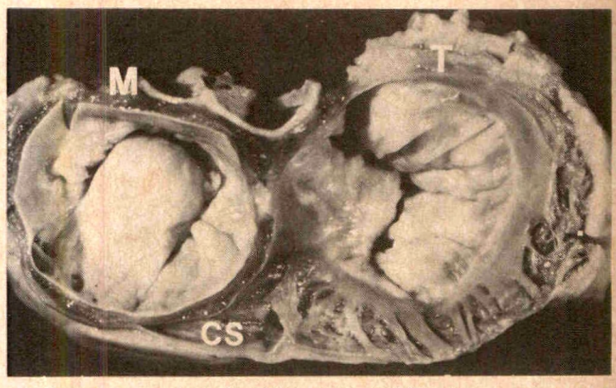

FIGURE 19. Prolapsing mitral (M) and tricuspid (T) valves from the atrial sides in a 55-year-old man (DCMEO #77-05-359) who died suddenly and unexpectedly while at a dance. The patient was known to have had a precordial systolic click and a late systolic murmur since age 36 years but had always been asymptomatic. The M-mode echocardiogram was typical of mitral prolapse. At necropsy, a huge prolapsing "scallop" of the posterior mitral leaflet was present and at least 1 chorda tendinea to this leaflet had ruptured. The leaflet area of the tricuspid valve also was considerably increased. CS = coronary sinus.

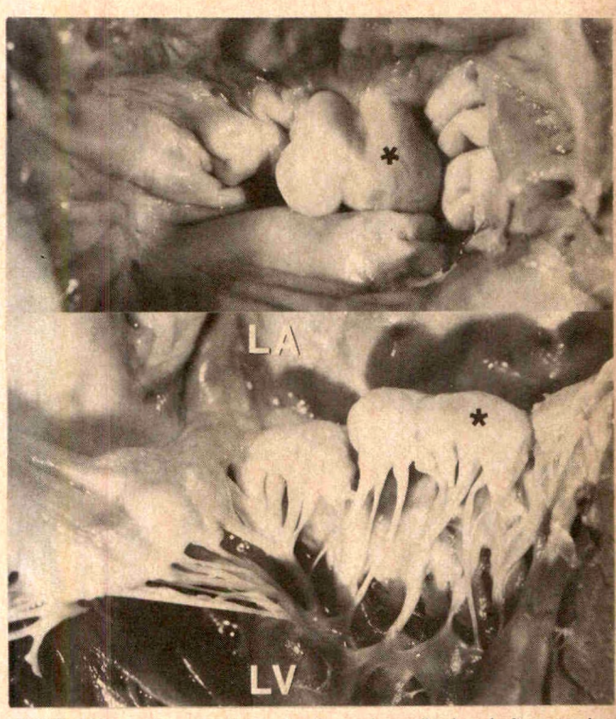

FIGURE 20. Prolapsed mitral valve from above (**top**) and after opening (**bottom**) in an 88-year-old woman who died when hit by an automobile. The patient had had no symptoms of cardiac dysfunction. The **asterisk** indicates the most prolapsed portion of posterior mitral leaflet. The mural endocarium beneath the posterior leaflet is thickened by fibrous tissue. LA = left atrium; LV = left ventricle.

echocardiograms; none demonstrated prolapse. Left ventriculograms, performed in all 97 patients, indicated prolapse in only 16 (27%) of the 60 prolapse patients and in none of the other 37 patients with other causes. Selective coronary angiograms were performed in 53 (55%) of the 97 patients. All 29 with MR secondary to coronary heart disease had significant (>50% diameter reduction) coronary narrowing demonstrated angiographically in at least 2 of the 3 major coronary arteries. Of the 60 patients with mitral prolapse, coronary angiograms were

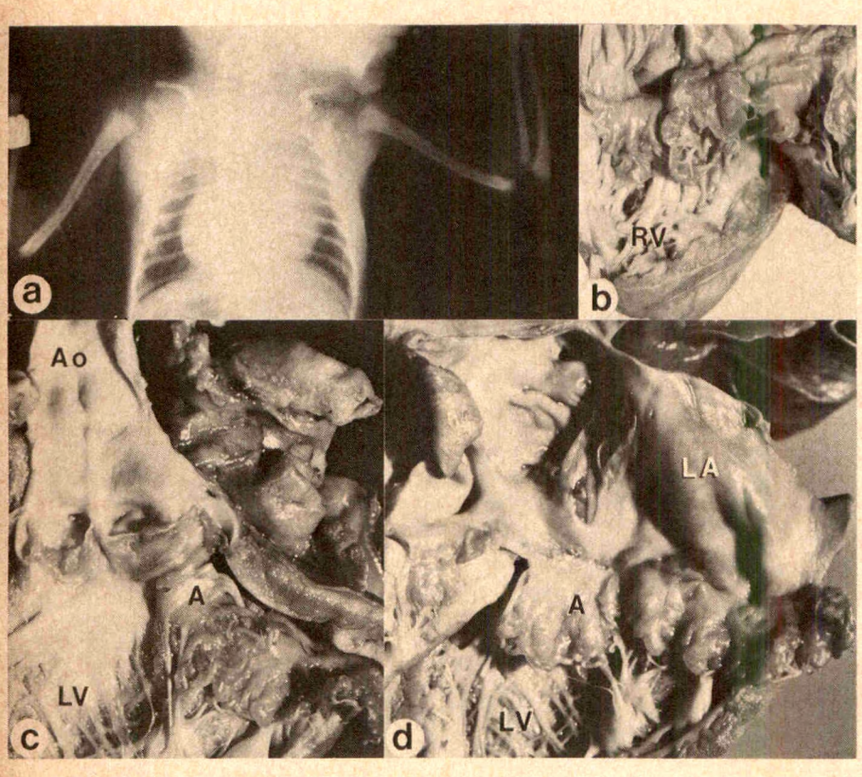

FIGURE 21. Congenital floppy mitral valve and floppy tricuspid valve in a 2-day-old boy (A67-236) who had long toes and fingers, a high-arched palate, and a grade 3/6 precordial systolic murmur typical of mitral regurgitation when examined. The heart was enlarged (**a**) and the infant died of congestive cardiac failure. At necropsy, the intima of the ascending aorta (Ao) was wrinkled (**c**), suggesting that the underlying media was abnormal at this early stage. Shown here are the opened aorta, aortic valve, and left ventricle (LV). A = anterior mitral leaflet. **d,** opened left atrium (LA), mitral valve, and left ventricle (LV). The mitral leaflets are considerably elongated in both longitudinal and transverse dimensions. The left atrium is dilated. **b,** the tricuspid valve leaflets also are elongated in both transverse and longitudinal dimensions. RA = right atrium; RV = right ventricle. (Reprinted, by permission, from Roberts and Honig.[40])

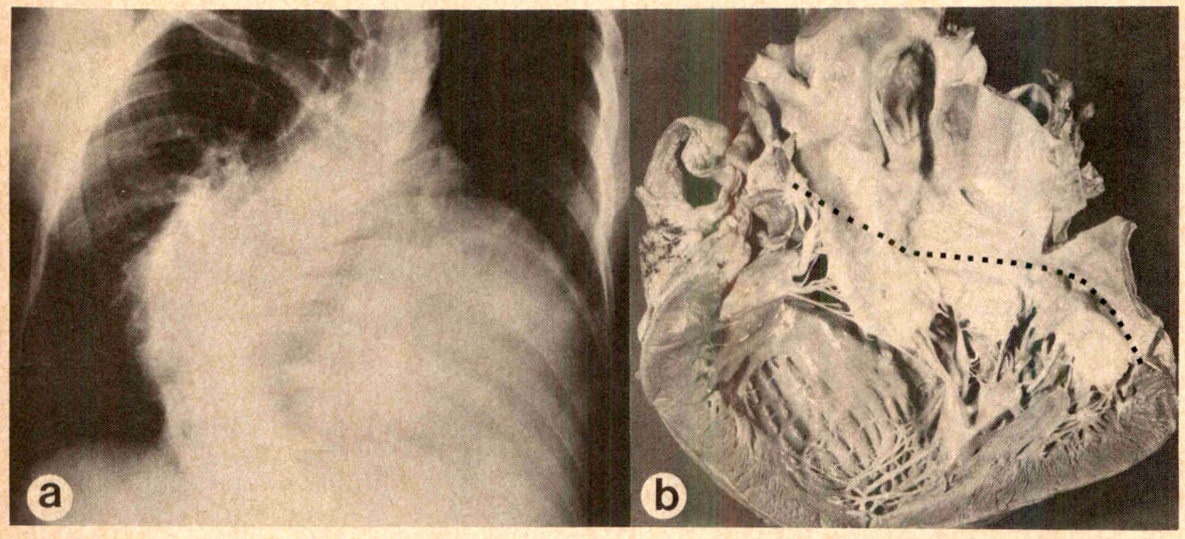

FIGURE 22. Posteroanterior chest roentgenogram (**left**) and opened left atrium, mitral valve, and left ventricle (**right**) in a 28-year-old man (A63-25) who had the onset of exertional dyspnea 4 years before death and evidence of overt congestive heart failure for 1 year before death. He never had a murmur of aortic regurgitation. At necropsy, the aorta was normal both grossly and histologically. The mitral valve anulus (**dotted line**) is greatly dilated (17 cm) and the length of the cusps from basal attachment to distal margin is elongated without elongation of the chordae tendineae. The vertebral column is greatly deformed (**left**). (Reprinted, by permission, from Roberts and Honig.[40])

performed in 23; only 3 (13%) had significant coronary narrowing, limited in each to 1 (right) coronary artery. Auscultation and hemodynamic data at cardiac catheterization were not helpful in delineating the origin of the MR. None of the 97 patients—including the 60 classified as having prolapse—had systolic clicks and the systolic precordial murmurs in all 97 patients were holosystolic. The average pulmonary arterial, left atrial (or pulmonary arterial wedge), and left ventricular pressures were similar in the 97 patients irrespective of the origin of the MR. The systolic systemic arterial pressures, however, were significantly higher in the patients with mitral prolapse and ruptured chordae tendineae than in those with mitral prolapse and intact chordae tendineae.

Surprisingly, few reports are available describing the various causes of MR in large numbers of patients. Furthermore, we[12] were unable to find any reports concerning the causes of pure MR in groups of patients in whom any associated MS or aortic valve dysfunction had been excluded by appropriate hemodynamic and angiographic studies. The most frequently cited report describing patients with MR appears to be that by Selzer and Katayama,[62] who summarized findings in

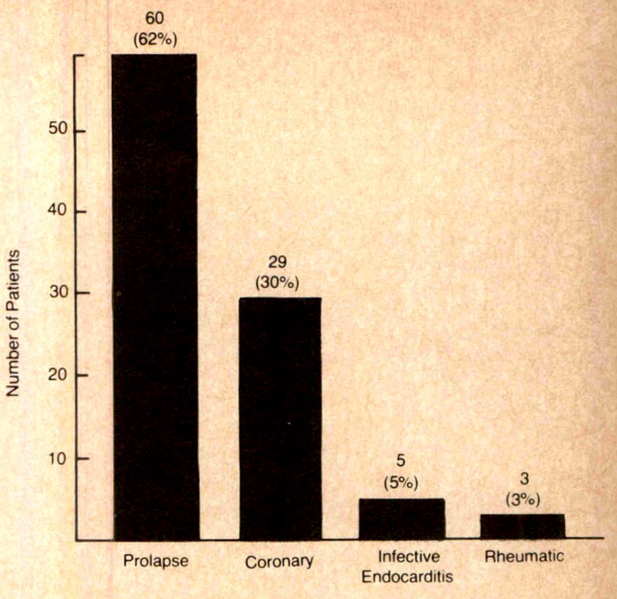

FIGURE 23. Bar graph showing the 4 conditions causing chronic, isolated, pure mitral regurgitation in 97 patients with operatively excised valves. (Reprinted, by permission, from Waller et al.[12])

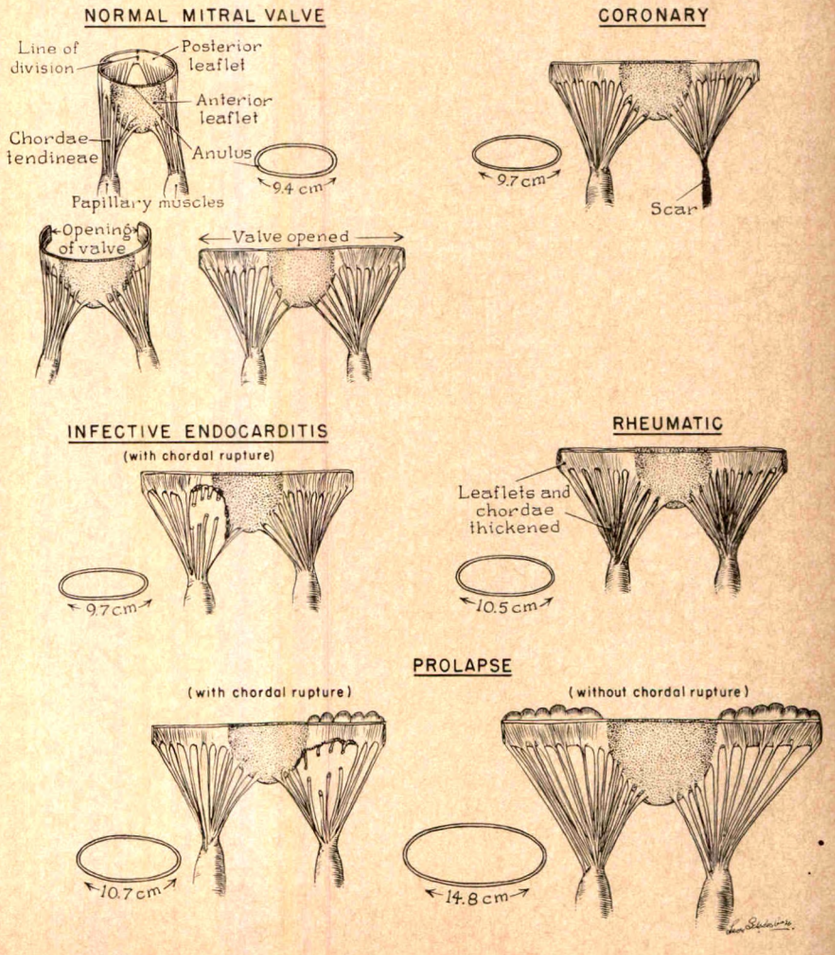

FIGURE 24. Diagram showing morphologic variations in mitral valve "anular" circumference and leaflet area in 4 conditions causing isolated, pure mitral regurgitation. (Reprinted, by permission, from Waller et al.[12])

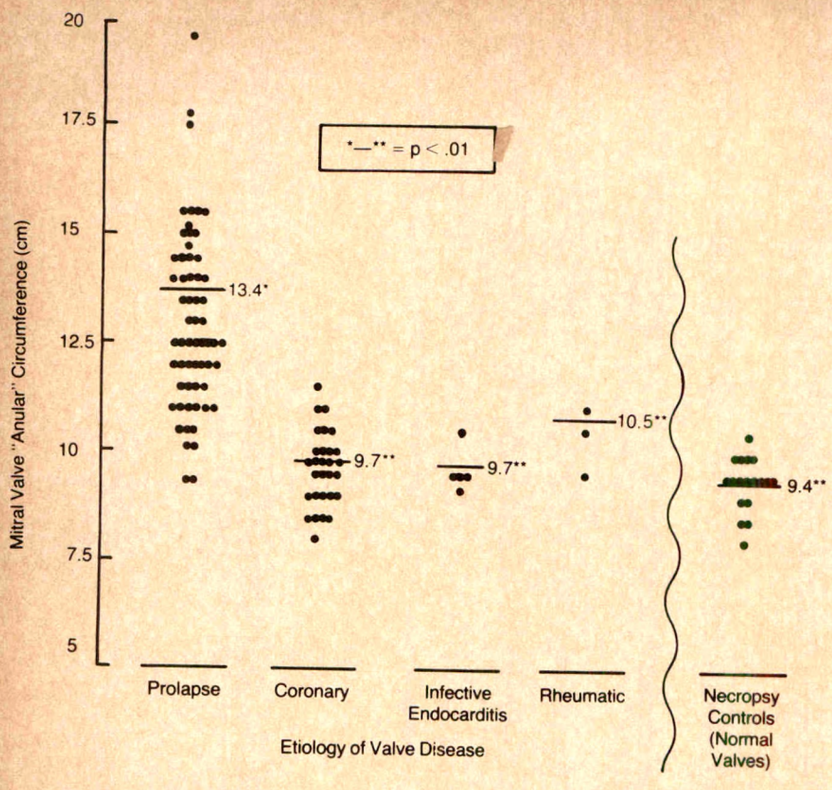

FIGURE 25. Graph showing mitral valve "anular" circumference (in centimeters) in each of the 97 patients with operatively excised mitral valves in the 4 conditions causing chronic, isolated, pure mitral regurgitation, and in 18 necropsy control valves. (Reprinted, by permission, from Waller et al.[12])

230 patients. Although 212 of their 230 patients had pure MR defined as the "absence of a late diastolic gradient across the valve . . . except in tachycardia" at the time of cardiac catheterization, some of their patients had MS at other times. Of their 230 patients, 88 were classified as having MR of rheumatic origin, and I suspect that nearly half (42 patients) had MS at some time in their course: 5 had had mitral commissurotomies for MS and severe MR developed subsequently; 8 of their rheumatic patients had MR only after the development of infective endocarditis, and it is probable that 1 or more previously had had MS; and 33 (38%) of their 88 rheumatic patients had sizeable calcific deposits in their mitral valves, a finding quite unusual in patients without some degree of MS. (Only 4 of our 97 patients had grossly visible calcific deposits in their excised mitral valves.) It is also difficult to compare the observations in our patients with those reported by Selzer and Katayama because of differences in patient selection. We[12] studied only patients who were in functional classes III and IV (New York Heart Association) because of congestive heart failure; all underwent mitral valve replacement and all had their valves examined by the same observer. Seventy (30%) of the 230 patients reported by Selzer and Katayama were in functional classes I or II, and mitral valve operations were performed in just over half of the 230 patients. Additionally, they included children, which we did not. Finally, we excluded patients with any aortic valve dysfunction, which may or may not have been the case in the study by Selzer and Katayama.

In the past, rheumatic heart disease has been considered the most common cause of severe MR, but it is likely that most or many patients so classified in older studies had some degree of MS. Because there has been such a strong tendency in the past to believe that severe MR was usually the result of rheumatic heart disease, other causes commonly have not been sought and definitions of "rheumatic" MR have not been precisely stated. Before 1963, most prolapsing or floppy mitral valves almost certainly were called "rheumatic" in origin at necropsy or operation. Our report[12] morphologically defined a prolapsed mitral valve which can cause severe MR; its anular circumference and leaflet area are clearly increased over that of other valves causing MR, except when the chordae tendineae of the prolapsing valve are ruptured. It is hoped that this definition will prevent indiscriminate labeling of mitral disease in the future as rheumatic when other evidences of previous rheumatic carditis are lacking.

Congenital MR is usually associated with other anomalities.[2,6,30–40] "*Isolated*" congenital MR is usually accompanied by *endocardial fibroelastosis of the left ventricle.* It is sometimes difficult, however, to determine what causes the mitral valve to be regurgitant in this circumstance. Neither is it always clear why the mitral valve is frequently regurgitant in patients with *partial atrioventricular canal* (endocardial cushion defect).[30,31,37] Nearly all patients with partial atrioventricular canal have a cleft, either partial or complete, in the anterior mitral leaflet. It would be easy to attribute the MR to the cleft, but the MR usually disap-

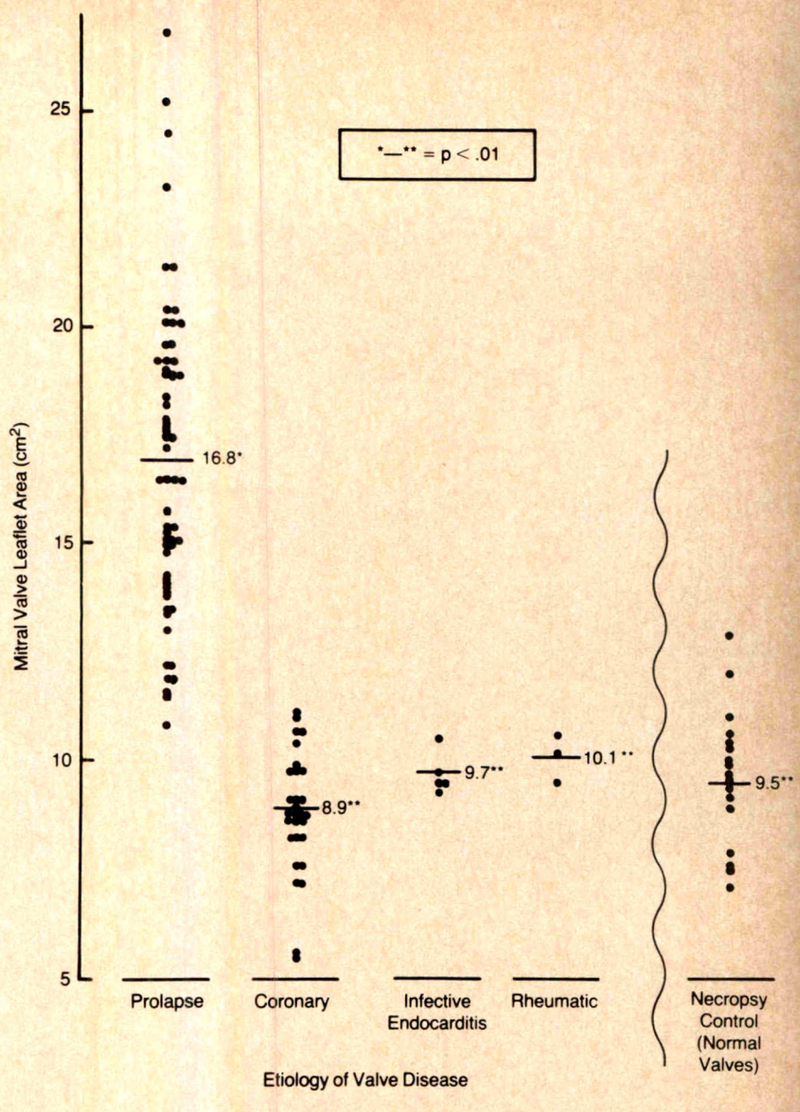

FIGURE 26. Graph showing mitral valve leaflet area (in centimeters squared) in each of the 97 patients with operatively excised mitral valves in the 4 conditions causing chronic, isolated, pure mitral regurgitation and in 18 necropsy control valves. (Reprinted, by permission, from Waller et al.[12])

pears after operative closure of the associated defect in the lowermost portion of the atrial septum (ostium primum defect), irrespective of whether the cleft in the anterior mitral leaflet is closed by suture. For the same reason, it is unlikely that the anomalous chordae tendineae that insert onto the crest of the ventricular septum play a significant role in the production of MR. It is helpful to think of partial atrioventricular canal as a syndrome consisting of 5 components: (1) defect in the lowermost portion of atrial septum; (2) cleft in the anterior mitral leaflet; (3) absence of tissue, either partial or complete, in the septal tricuspid valve leaflet; (4) anomalous chordae tendineae from the anterior mitral leaflet to the crest of ventricular septum; and (5) ventricular septal defect. The syndrome may include all 5 components or may have as few as 2; most commonly, the first 4 components are present. A cleft in the anterior mitral leaflet may occur, however, in the absence of a defect in the lowermost portion of the atrial septum.[63] These individuals usually present with evidence of isolated MR or with features of isolated ventricular septal defect. Of 21 necropsy patients with a cleft in the anterior mitral leaflet unassociated with a defect in the lowermost portion of the atrial septum reported by Segni and Edwards,[63] 11 had no defect in any portion of the atrial or ventricular septa and the other 9 had associated defects, usually ventricular septal defect or a fossa ovale type atrial septal defect or both. Occasionally, the ostium primum defect may be so small that the shunt through it is missed or is only trivial; these patients also may present with essentially pure MR.[30,31]

Corrected transposition is an entity that has produced much confusion. Corrected transposition and complete transposition are quite different; the only thing they have in common is the word "transposition." Complete transposition is essentially 1 defect: the great arteries are transposed, so that the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle. In corrected transposition, the great arteries

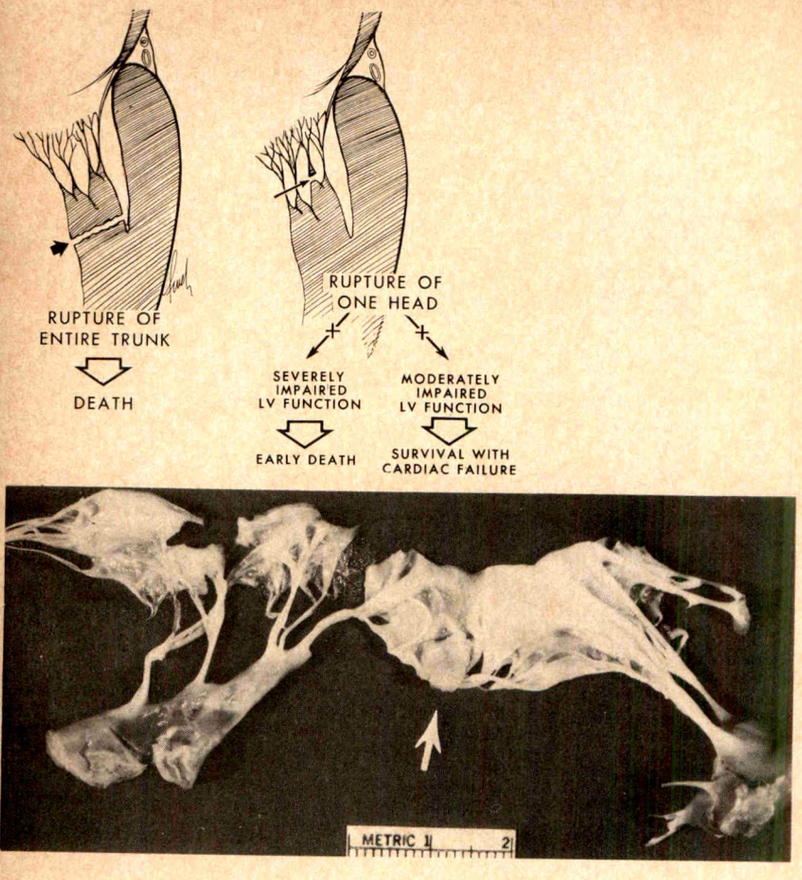

FIGURE 27. Top, diagram of the types of, and possible consequences of, papillary muscle rupture during acute myocardial infarction. It is likely that rupture of the entire trunk (**left**) is incompatible with survival in any patient since a major portion of the support to both valve leaflets is destroyed. With rupture of an apical head (**right**), survival would appear to depend on the extent to which the function of the left ventricle has been impaired by the infarct. With severely impaired ventricular function, the additional burden of even modest mitral regurgitation may be intolerable, and death will ensue. If the left ventricle is less severely compromised, survival is possible for weeks or months, but congestive cardiac failure will almost invariably develop. **Bottom,** rupture of a portion of 1 papillary muscle during acute myocardial infarction in a 51-year-old man (S67-813) who underwent mitral valve replacement 3 months after the onset of the infarction. Preoperatively, the pulmonary arterial pressure was 60/28 mm Hg; pulmonary arterial wedge pressure, mean 28, v42; left ventricular pressure 74/17 mm Hg; and cardiac index, 1.7 liters/min/m^2. The leaflets are normal but the posteromedial papillary muscle is necrotic and fibrotic and a portion of it (**arrow**) is entwined in chordae tendineae at the margin of the anterior mitral leaflet. This is a view of the ventricular aspects of the leaflets. LV = left ventricular. (Reprinted, by permission, from Roberts and Perloff.[2])

also are transposed, but, in addition, the ventricles, atrioventricular valves, coronary arteries, and conduction system are inverted. Patients with complete transposition die because they have inadequate communications between the 2 circuits. Patients with corrected transposition theoretically should be able to live a full lifespan, but usually this is not the case because associated defects—namely, ventricular septal defect or regurgitation of the left-sided atrioventricular valve, or both—cause the heart to function abnormally. Abnormalities of the left-sided atrioventricular valve, a systemic valve but anatomically a tricuspid valve, are the most common associated anomalies in corrected transposition.[64] Of the anomalies, the most frequent is the Ebstein-type malformation. These valves are intrinsically regurgitant because the chordae are short and the leaflets are closely adherent to the ventricular endocardium.

A mitral valve may be abnormal anatomically and yet function entirely normally. A congenital malformation illustrating this point is the *double-orifice mitral valve*, which looks like a double-barreled shotgun.[65] Generally, both orifices are totally competent and the patient should be asymptomatic.

Papillary Muscle Dysfunction

Rupture of a portion of a papillary muscle was not appreciated until 15 years ago.[48] The original concept of papillary muscle rupture was rupture of its entire trunk, caused either by myocardial infarction from coronary narrowing or by trauma (Fig. 27). Complete transsection of a left ventricular papillary muscle is incompatible with life because about 60 chordae tendineae are thus disrupted. More frequent is rupture of a portion of a papillary muscle. In this situation, the largest amount of MR is probably caused by the rupture, but all these patients have severe necrosis of the remaining portion of the papillary muscle and the latter probably contributes to the regurgitation. When 1 head of a papillary muscle is ruptured, about 10 third-order chordae tendineae are disrupted.

Necrosis or fibrosis of a papillary muscle without rupture is far more common than rupture. Table II lists conditions frequently associated with papillary muscle dysfunction, particularly necrosis or fibrosis.[3] Although coronary arterial luminal narrowing is the most frequent cause of papillary muscle necrosis or fibrosis, many other conditions may be accompanied by papillary muscle lesions. The papillary muscles are fibrotic or necrotic in so many conditions because they are the last structures in the heart to be perfused by arterial blood. Of the 2 left ventricular papillary muscles, the posteromedial one has the poorer blood supply, and, consequently, lesions are more frequent in it than in the anterolateral muscle. The posteromedial muscle receives its oxygen mainly from blood passing through the right coronary artery. The mouth of this artery may be >15 cm from the apex of the posteromedial muscle. To perfuse it, blood must pass through the entire thickness of left ventricular wall, turn uphill (so to speak), and

ascend a distance equivalent to 2 more full thicknesses of left ventricular wall. Thus, the apices of the papillary muscles are the sites farthest from the coronary ostia, and they receive oxygen only after the other myocardium has had an opportunity to extract its oxygen needs. Although the surfaces of the papillary muscles are entirely bathed by intracavitary ventricular blood, only a small amount of oxygen diffuses into these structures from the intracavitary blood.

The most common cause of papillary muscle necrosis or fibrosis is *narrowing of the coronary arterial lumen by atherosclerotic plaques.* The posteromedial papillary muscle is usually involved in acute posterior myocardial infarction. In anterior wall infarction, however, the anterolateral papillary muscle may be spared, presumably because its blood supply is better than that of the posteromedial muscle. Since infarction limited to the ventricular septum or to the lateral portion of the left ventricular free wall (that is, the portions of the left ventricular wall unassociated with papillary muscles) is rare, the papillary muscles are usually involved when myocardial infarction occurs. It is, therefore, surprising that papillary muscle dysfunction is not more frequent during or after acute myocardial infarction.

In patients with *left ventricular outflow obstruction*, lesions often occur in the papillary muscles. Valvular aortic stenosis, whether in infants or in adults, when superimposed on a congenitally malformed valve, either unicuspid or bicuspid, is nearly always associated with fibrosis and atrophy of at least the posteromedial papillary muscle. Rheumatic valvular aortic stenosis combined with organic MS or MR, however, infrequently is associated with papillary muscle fibrosis or atrophy. Nearly all adult patients with discrete subaortic stenosis or hypertrophic cardiomyopathy with or without diffuse subaortic stenosis have small fibrous scars in both left ventricular papillary muscles, but atrophy of 1 or both muscles is uncommon.[39]

Foci of necrosis also are common in patients with fatal *severe valvular regurgitation of recent onset.* Among 47 patients dying of active valvular infective endocarditis and examined personally, 34 (72%) had necrotic lesions in 1 or both left ventricular papillary muscles; none had significant narrowing of the extramural coronary arteries. Most patients had pure aortic regurgitation, but some had pure MR secondary to the active infective endocarditis. Severely diminished cardiac output resulting in poor myocardial perfusion was believed the cause of the papillary muscle necrosis in these patients.

Small fibrous scars in the papillary muscles are common in patients with *systemic hypertension*, but atrophy of these muscles is infrequent in this condition, unless coronary heart disease also is present. In left ventricular hypertrophy of any cause, the hypertrophy of the papillary muscles should probably be proportional to that of the left ventricular free wall or ventricular septum. This proportional hypertrophy usually exists in patients with systemic hypertension but is infrequent in patients with left ventricular outflow obstruction.

Fibrosis with atrophy of the papillary muscles is to be expected in patients with primary *endocardial fibroelastosis* of the left ventricle. Histologically, the thickened endocardium in this condition is similar to the media of the aorta, being characterized by elastic fibrils running parallel to one another and to the surface. Primary left ventricular endocardial fibroelastosis may be an anatomic expression of chronically inadequate coronary arterial perfusion of the left ventricle; since the posteromedial papillary muscle is the least well-perfused portion of the heart, this structure is affected the most. In the congenital anomaly, origin of the left or both coronary arteries from the pulmonary trunk, diffuse endocardial fibroelastosis of the left ventricle is nearly always an associated lesion.[33] Fibrosis and atrophy of the left ventricular papillary muscles are to be expected in this anomaly, and these patients may present clinically with features of pure MR.

Foci of fibrosis or necrosis in the left ventricular papillary muscles are infrequent in patients with dilated cardiomyopathy.[54,66] Rarely, *myocarditis* may be localized to papillary muscle and adjacent left ventricular free wall.[67] Patients with the *neurogenic heart diseases* (Friedreich's ataxia, progressive muscular dystrophy, and myotonic muscular dystrophy) generally have scarred left ventricular papillary muscles, especially the posteromedial ones.[68] The African cardiomyopathy, *endomyocardial fibrosis*, may be associated with extensive scarring of the papillary muscles.[54] In this condition the posteromedial muscle is usually covered by a thrombus or by dense fibrous tissue that probably represents organized thrombus. Likewise, *Löffler's fibroplastic parietal endocarditis*, which may be 1 stage of endomyocardial fibrosis,[53] is usually associated with extensive scarring of 1 or both papillary muscles.

The papillary muscles are subject to various infiltrative processes, just like any other portion of myo-

TABLE II Spectrum of Left Ventricular Papillary Muscle Dysfunction

I. Rupture of papillary muscle
  A. Total ("belly" or trunk)
    1. Rapid death
    2. Survival—not described
  B. Partial ("head")
    1. Rapid death
    2. Survival but chronic congestive cardiac failure
II. Fibrosis or necrosis of papillary muscle without rupture
  A. With coronary arterial narrowing
    1. Acute myocardial infarct
    2. Healed myocardial infarct
  B. Without coronary arterial narrowing
    1. Acute
    2. Chronic
      a. Valvular, subvalvular (discrete and diffuse) and supravalvular aortic stenosis
      b. Systemic hypertension
      c. Origin of left coronary artery from pulmonary trunk
      d. Primary endocardial fibroelastosis
      e. Endomyocardial fibrosis
      f. Löffler's fibroplastic parietal endocarditis
      g. Diffuse (primary) myocardial disease
      h. Focal myocardial disease
        1. Idiopathic
        2. "Neurogenic" heart disease
        3. Infectious
III. Normal or near-normal papillary muscles but severe fibrosis or necrosis in adjacent left ventricular free wall with and without coronary arterial narrowing

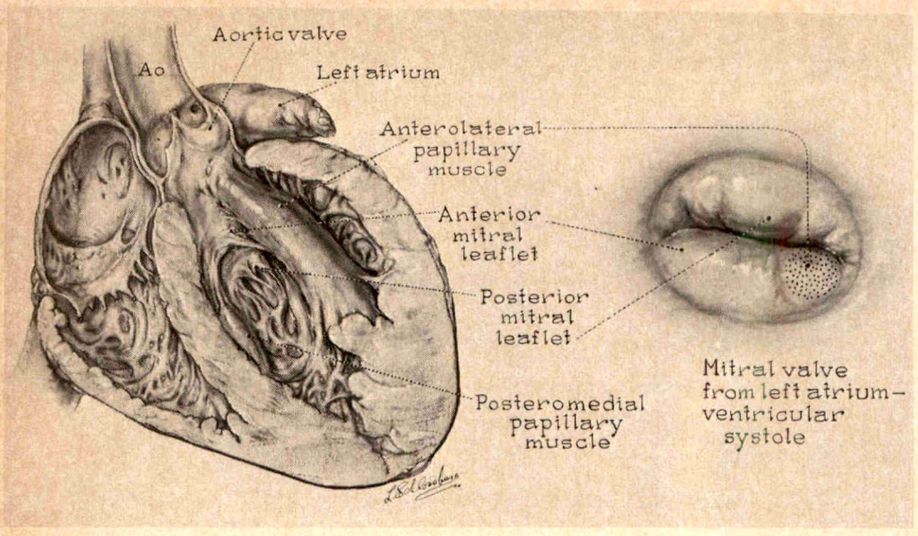

FIGURE 28. Drawing of heart in a 23-year-old man (DCMEO #80-02-134) who died from idiopathic dilated cardiomyopathy. An incidental finding at necropsy was the insertion of the anterolateral papillary muscle directly onto the anterior mitral leaflet. This congenital anomaly has been observed personally in about 5 cases at necropsy. It appears to have no functional significance. Ao = aorta.

cardium. *Pyogenic abscesses*, *Aschoff bodies*, *granulomas*,[67] *neoplasms*,[69–71] *amyloid*,[72] *iron*,[73] *and air*[74] have all been observed in these structures. Congestive heart failure from severe MR may be the initial symptom of cardiac *sarcoidosis*.[67]

The most frequent congenital malformation of papillary muscles is the occurrence of only 1 such muscle in the left ventricle. In this condition, described as the *parachute mitral valve*, all mitral chordae tendineae are attached to the 1 left ventricular papillary muscle (Fig. 11). The resulting mitral valve is usually stenotic, but it may be purely regurgitant or it may function normally.[35] The single papillary muscle is usually associated with other malformations, including a supramitral valve ring, diffuse subaortic stenosis, and coarctation of the aorta. Other malformations, including valvular aortic stenosis, ventricular septal defect, and valvular pulmonic stenosis, also may occur.

There may be not only 1 too few papillary muscles but also 1 too many. An *accessory papillary muscle* is usually of no functional significance, but it has been seen in association with congenital MR. When 2 papillary muscles are present, 1 or both may still be congenitally malformed. One or both papillary muscles may be abnormally large and malpositioned with attachment onto the anterior mitral leaflet, creating the potential at least for valvular stenosis or regurgitation (Fig. 28). Both papillary muscles also may be poorly developed and small. This finding is particularly characteristic with origin of the left coronary artery or both coronary arteries from the pulmonary trunk. In this situation, the papillary muscles arise more cephalad than normal from the left ventricular free wall.

Both left ventricular papillary muscles usually are excised either completely or incompletely at operations to replace the mitral valve. The myocardium of the free wall at the sites of excision of these muscles is always infiltrated by inflammatory cells when this area is examined in the early postoperative period. With time, these areas are covered by dense fibroelastic tissue simulating the composition of the media of the aorta. If the papillary muscles are not excised when the mitral leaflets and chordae tendineae are excised during mitral valve replacement, the papillary muscles atrophy and are focally replaced by fibrous tissue; the myocardial cells become disorganized.[75] When the papillary muscles are excised at operation, each is grasped by a clamp extending through the mitral orifice from the left atrium. If the papillary muscles are pulled too vigorously by the clamp during their excision, portions of left ventricular free wall also may be excised. The result may be perforation or severe thinning of the left ventricular wall. The latter may lead to the formation of a functioning or anatomic aneurysm or both.[76,77]

Mitral Anulus

Although it may accompany left ventricular dilation, mitral anular dilation, except in patients with prolapsing or floppy mitral valves,[12] is a rare cause of MR[59]; in the past, most patients with MR that was believed the result of mitral anular dilation probably had papillary muscle dysfunction. Mitral anular dilation to a degree capable of causing MR probably does not occur except in association with mitral valve prolapse because the surface area of the mitral leaflets is more than twice the area of the mitral orifice, and the anulus contracts during ventricular systole.[2] The mitral ring has a sphincter-like action because the mitral orifice is smaller during ventricular systole than during diastole. In patients with dilated left ventricles, the widest diameter does not occur at the left ventricular base, the area that includes the mitral anulus, but in the midportion of the chamber between apex and base (Fig. 29). In fact, the base of the left ventricle is prevented from dilating freely because the "fibrous skeleton" is attached to it, whereas the midportion of the left ventricle is not so restricted. Indeed, severe left ventricular dilation may occur without any dilation of the mitral anulus.

Although it is now well known that MR may occur in patients with dilated left ventricles from any cause

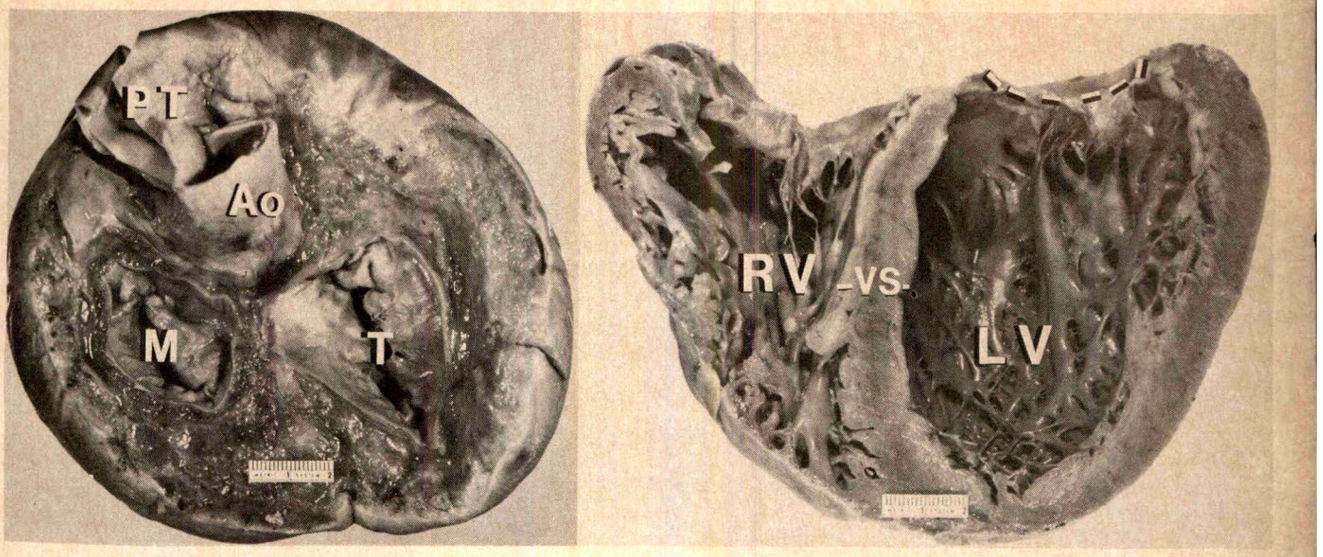

FIGURE 29. The heart of a 34-year-old man (DCGH #74A-65) with idiopathic dilated cardiomyopathy and clinical evidence of both tricuspid and mitral regurgitation of severe degree. Both ventricles are considerably dilated. The greatest increase in dimension of the right (RV) is in the area of the tricuspid valve anulus. The tricuspid valve orifice (T) admitted 4 fingers readily, indicating its proximal diameter to be about 8 cm. In contrast, the maximal diameter of the left ventricle (LV) was about midway between the apex and the mitral anulus. The mitral orifice (M) only admitted 2 fingers, indicating that its maximal diameter was about 4 cm. The mitral regurgitation resulted, therefore, not from anular dilatation, which was mild, but probably from altered angulation of the left ventricular papillary muscles. Ao = aorta.

without associated left ventricular necrosis or fibrosis, it is less well recognized that necrosis or fibrosis of the left ventricular free wall, unassociated with left ventricular dilation or papillary muscle or mitral tissue lesions, also may be associated with MR. Generally, the scarring or necrosis of the myocardium adjacent to the papillary muscles fails to move or moves paradoxically during ventricular systole, and the abnormal ventricular contraction may lead to abnormal papillary muscle anchoring, resulting in MR. Anatomic left ventricular aneurysms unassociated with papillary muscle necrosis or fibrosis may cause MR by the same mechanism.

Abnormal pulling on the papillary muscles unassociated with left ventricular necrosis or fibrosis or cavity

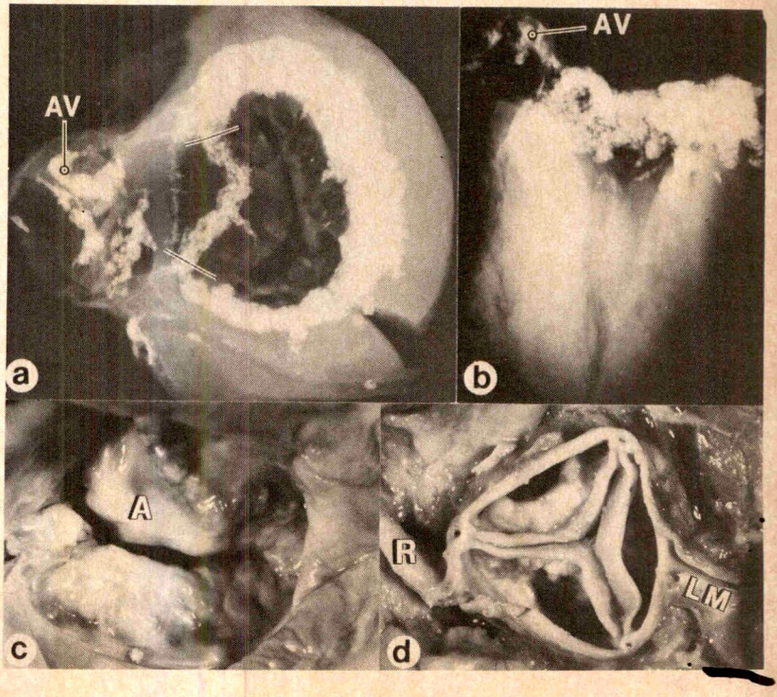

FIGURE 30. Massive calcific deposits in the mitral anulus (**a, b,** and **c**), aortic valve (AV) (**a, b,** and **d**), and coronary arteries (**a** and **b**) in an 82-year-old man (NNMC #A70-200) who had Paget's disease of bone. The short bar of calcium between the lines in **a** is that extending across the anterior (A) mitral leaflet. The radiogram in **a** is a cephalad-caudal orientation, and that in **b,** a lateral view. The mitral valve as observed from the left atrium is shown in **c,** and the aortic valve from the aorta in **d.** LM and R = left main and right coronary arteries. (Reprinted, by permission, from Roberts and Waller.[79])

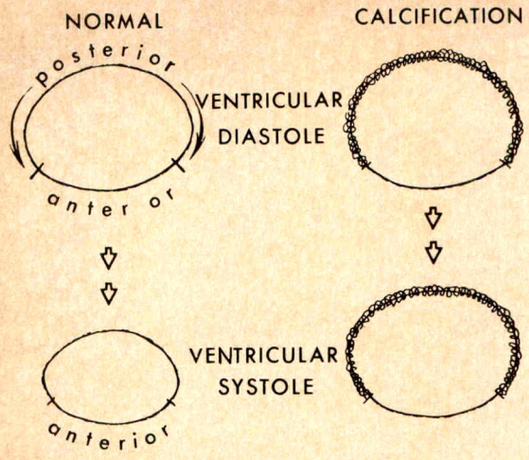

FIGURE 31. Mechanism of mitral regurgitation in patients with calcification of the mitral anulus. During ventricular systole, the base of the left ventricle contracts like a sphincter. Included in the base of the left ventricle is the anulus behind the posterior mitral leaflet. Thus, this circumference decreases during systole. If, however, the anulus behind the posterior mitral leaflet is calcified, the sphincter-like contraction of the left ventricular base may be prevented from occurring. The area of the mitral orifice thus is not decreased, and mild degrees of mitral regurgitation may result. (Reprinted, by permission, from Roberts and Perloff.[2])

dilation may occur in patients with *hypertrophic cardiomyopathy*; this mechanism may account for their MR.[51,54] The huge thickening of the ventricular septum may distort or bend the anterolateral papillary muscle and prevent proper contraction of this structure during ventricular systole. In addition to actual bending of the anterolateral left ventricular papillary muscle, however, the mitral leaflets in adults with hypertrophic cardiomyopathy are always thickened. The thickening of the anterior mitral leaflet appears to be the result of its contact with the mural endocardium in the left ventricular outflow tract during ventricular systole. But the posterior mitral leaflet also is thickened, probably a result of its contacting itself abnormally during ventricular systole. The mitral leaflets and chordae tendineae are within the left ventricular cavity, which in hypertrophic cardiomyopathy is relatively small; as a consequence, space within the left ventricle may be inadequate to easily accommodate the mitral leaflets and chordae, and with vigorous contractions portions of the posterior leaflet contact other portions of the same leaflet abnormally. Fibrous thickening is the consequence. The MR in hypertrophic cardiomyopathy usually disappears after operative excision or incision of myocardium in the left ventricular outflow tract.[51]

Calcification of the mitral anulus is one of the more frequent abnormalities of the heart. Mitral anular calcification is generally considered to be a disease of elderly women. Indeed, of 14 patients with "massive" mitral anular calcification reported by Korn et al[78] 21 years ago, all were women and all were over 65 years of age. It is incorrect, however, to believe that this entity is reserved for a particular sex at a particular time in life. During the past 14 years I have examined over 300 patients with mitral anular calcium at necropsy. Of the first 200 analyzed systematically, 47% were men and 53% were women. Of the 200 patients, 141 (70%) were over age 65 years and 17 (8%) were aged 45 years or less. The extent of the mitral anular calcium was graded 1^+ to 4^+: in 110 patients (55%) the deposits were graded 1^+ or 2^+ and in 90 patients (45%) grade 3^+ or 4^+. The calcium in 198 patients was limited to the anular region behind posterior mitral leaflet, usually forming a C-shaped configuration; in 2 patients, the calcium extended across the anterior mitral leaflet to form an O-shaped configuration[79] (Fig. 30). Of the 38 patients with 4^+ deposits, 76% were women. Thus, although mitral anular calcium of any degree appears to occur with similar frequency in men and women, the larger deposits (those likely to be seen on the chest roentgenogram) are more frequent in women. Calcium deposits also were present on the aortic aspects of the aortic valve cusps in 138 (69%) of the 200 patients (64 [32%] of whom had aortic valve stenosis) and in the coronary arteries in 168 (84%) patients.

Factors predisposing to mitral anular calcium were found in 80% of the 200 patients. These included elevation (>140 mm Hg) of left ventricular systolic pressure (142 patients), diabetes mellitus (39 patients), chronic hypercalcemia (9 patients),[80] prolapsing mitral valve (6 patients), the Marfan syndrome (5 patients),[40] left-to-right shunt (secundum type atrial septal defect) (3 patients), and the Hurler syndrome (2 patients).[46] Mitral anular calcium also may form late at sites of attachment of prosthetic mitral valves.[81]

The association of mitral anular calcium with calcific deposits in the coronary arteries and aortic valve cusps, the lack of mitral anular deposits in persons living in environments where the total serum cholesterol is ≤150 mg/dl, and the frequent occurrence of factors predisposing to atherosclerosis in patients with mitral anular calcium supports a common etiologic basis for both mitral anular calcium and atherosclerosis.

The functional consequences of mitral anular calcium are 2, namely MR or MS, and rarely, if ever, both. The presence of either MR or MS is a function of the amount of anular calcium present and also probably the size of the left ventricular cavity. The most common functional consequence, of course, is MR, which is nearly always of only mild degree and never of severe degree except in a patient with associated mitral anular dilatation in the setting of mitral valve prolapse.[12] The frequency of a murmur typical of MR is nearly always present in patients with $4^+/4^+$ anular deposits and is rarely the consequence of anular deposits if the extent of the latter is only $1^+/4^+$. The mechanism of MR in patients with mitral anular calcium is depicted graphically in Figure 31. Mitral stenosis as a consequence of mitral anular calcium has been observed only in the presence of huge ($4^+/4^+$) mitral anular deposits associated with severe left ventricular hypertrophy without dilatation, usually the consequence of associated left ventricular outflow obstruction.[25]

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Improved Cross-Sectional Echocardiographic Technique For Visualization of the Retrocardiac Descending Aorta In Its Long Axis

Normal Findings and Abnormalities in Saccular And/or Dissecting Aneurysms

PATRICIA C. COME, MD

The feasibility of using an improved ultrasonic technique for visualization of the retrocardiac descending thoracic aorta was studied in 50 consecutive patients. Both anterior and posterior aortic walls were well delineated in long as well as short axis in 92%. The mean length of the visualized portion of the retrocardiac aorta was 8.4 cm (range 4.5 to 13) and exceeded 6 cm in 40 of 46 patients. The mean diameter was 2.0 cm (range 1.3 to 2.7).

Five patients with saccular (1 patient) and/or dissecting (all 5 patients) aneurysms involving the retrocardiac aorta were also examined. Abnormalities essentially identical to those seen with computerized tomography and aortography were noted. Intimal flaps were visualized by ultrasound in all 5 patients and were seen to oscillate reproducibly with the cardiac cycle, suggesting differential rates of filling of false and true lumens.

This and other previous cross-sectional echocardiographic studies of the ascending aorta suggest that ultrasound may be useful in the initial evaluation of patients presenting with symptoms or signs suggestive of acute or chronic aortic disease.

Cross-sectional echocardiography has permitted recognition of a variety of aortic abnormalities, including supravalvular aortic stenosis, aortic aneurysms, and coarctation.[1–8] While recognition of the retrocardiac portion of the descending aorta has been described,[5–7,9] diagnosis of abnormalities in that region has been considered more difficult than recognition of aortic root disease.

This prospective study was designed to assess the usefulness of a new echocardiographic technique in defining the retrocardiac descending aorta in its long and short axes. It reports the echocardiographic findings in 50 consecutive patients. In addition, the echocardiographic features of 5 patients with retrocardiac expanding or dissecting aortic aneurysms, or both, are described.

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Methods

Fifty consecutive patients, without apparent aortic disease, were studied in the supine and 30° left lateral positions using a Hoffrel 201A/514 mechanical sector scanner. With the transducer in the third or fourth intercostal space just to the left of the sternum, the descending thoracic aorta was identified in its short axis as a circular structure posterior to the left atrium, to the atrioventricular groove, or to the left ventricle. The transducer was then rotated, generally approximately 90°, in an effort to visualize the descending aorta in its long axis. If optimal longitudinal visualization of the aorta was not obtained, the transducer was then moved laterally, and repeated attempts were made to visualize the descending aorta in its short and, subsequently, long axis. The identification of the descending aorta has been verified in our laboratory by injection of saline solution microbubbles into the aorta at the time of cardiac catheterization.

Results

The 50 consecutive patients had a mean age of 56 years (range 15 to 92) and included 25 females and 25 males. Both the anterior and the posterior walls of the retrocardiac descending thoracic aorta were cl[illegible]

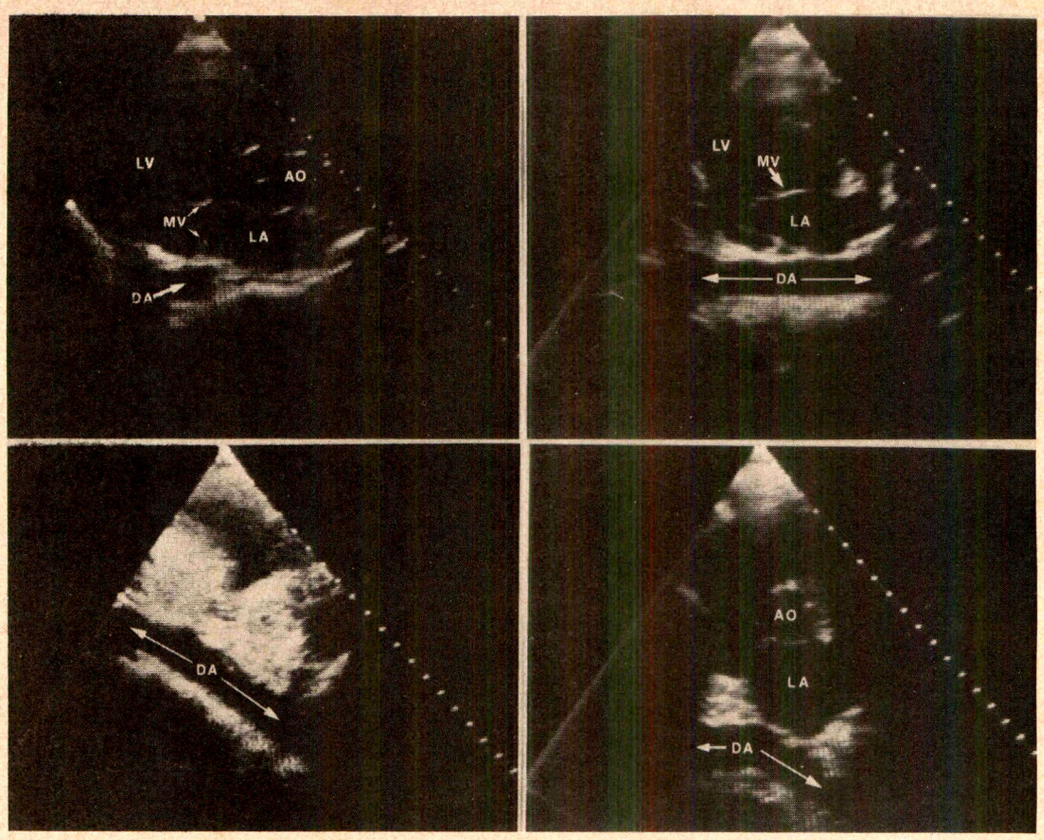

FIGURE 1. Representative cross-sectional echocardiograms obtained in a consecutive series of patients without signs or symptoms of dissection. The technique of visualizing the descending thoracic aorta (DA) is illustrated in the **upper panels.** The DA is first identified in its short axis (**top left**) as a relatively circular structure lying posterior to the junction of the left atrium (LA) and left ventricle (LV). The simultaneously obtained long-axis view of the heart is suboptimal since the transducer was placed several centimeters to the left of the sternum. The DA in its long axis is then obtained by rotation of the transducer approximately 90° from the position of short-axis study (**top right**). The aortic walls are seen to be smooth in this study obtained from a 15-year-old boy. In another patient, aged 88 years, the aortic walls are seen to be less smooth (**bottom left**), suggesting wall irregularities which might potentially arise from atherosclerotic placques. While the DA is generally seen to be a relatively straight, tubular structure, it was observed to be curved in its course in 1 patient, an 83-year-old woman with left atrial enlargement due to rheumatic mitral valve disease (**bottom right**). The left atrial enlargement was likely responsible for the deviation of the course of the DA in this patient. One centimeter markings are displayed on the right side of the sector. AO = aorta; MV = mitral valve.

visualized in long and short axis in 46 (92%). Optimal visualization always required transducer placement at least several centimeters to the left of the sternum, generally at the midclavicular line, and occasionally as far left as the anterior axillary line. In 1 other patient, a longitudinal structure thought to represent the aorta was visualized, but clear transition from the short- to long-axis views of the aorta could not be obtained by rotation of the transducer. The mean length of the aorta visualized was 8.4 cm (range 4.5 to 13) and exceeded 6 cm in 40 patients. Diameter ranged from 1.3 to 2.7 cm (mean 2.0). In its long axis, the aorta generally was a straight tubular structure with parallel walls (Fig. 1). In 1 patient with left atrial enlargement, however, the aorta curved around an enlarged left atrium (Fig. 1). While the anterior and posterior aortic walls generally appeared smooth in young patients, shagginess was often apparent in elderly individuals (Fig. 1). In none of the consecutive patients was there a stationary or oscillating linear echo suspicious for an intimal flap or change in aortic diameter suggestive of a saccular aneurysm.

Patients with aortic aneurysms involving the descending aorta: Five patients with saccular or dissecting aneurysms, or both, involving the retrocardiac descending aorta underwent ultrasound examination. Their clinical features, echocardiographic findings, and abnormalities documented by computerized tomography or aortography are shown in Table I. Figures 2 and 3 illustrate the representative 2-dimensional and M-mode echocardiographic findings. The echocardiographic studies and diagnosis of aortic disease preceded angiographic and tomographic confirmation in 4 patients and followed aortography in the fifth. In each of the 5 cases, the results of ultrasound evaluation were identical to those obtained by aortography or computerized tomography and permitted accurate classification of the aortic dissections into DeBakey types 1 or 3.

Discussion

The development of cross-sectional echocardiography has increased ultrasonic recognition of pathologic abnormalities of the thoracic aorta. The technique described here, and illustrated in 1 patient in a previous

TABLE I Clinical Features of Patients With Aortic Disease

Case	Age (yr) & Sex	Back Pain	Chest Pain	Echocardiogram: Aortic Root Diameter (cm)	Echocardiogram: Intimal Flap: Asc Ao	Echocardiogram: Intimal Flap: Des Th Ao	Type of DeBakey Dissection by Aortogram or Computerized Tomography	AR
1	68M	+	0	4.8	+	+*	I	0
2	51F	+	0	5.5	+	+	I	+
3	65M	+	+	4.0	0	+	III	0
4	63M	+	+	3.4	0	+*	III	0
5	87F	0	0	4.5	0	?	III†	0

* Stationary internal echo.
† Asymptomatic 8.0 cm in diameter aneurysm arising from descending thoracic aorta.
AR = aortic regurgitation; Asc Ao = ascending aorta; Des Th Ao = descending thoracic aorta.

report,[6] was developed to permit optimal visualization of the retrocardiac descending thoracic aorta in its long axis. While the descending aorta in its short axis can usually be visualized behind the left ventricle, the left atrium, or the atrioventricular groove with the transducer placed in the usual position for a long-axis study of the heart, this position rarely permits optimal examination of the retrocardiac aorta in its long axis and may explain the difficulty experienced by others in identifying pathology of the retrocardiac aorta. Movement of the transducer a number of centimeters to the left of the sternum in the third to fifth intercostal space, occasionally as far laterally as the midclavicular or anterior axillary lines, will, however, permit good visualization of this part of the aorta in the vast majority of patients. In each of our patients with descending aortic pathology, such a transducer position permitted recognition of a dissecting or expanding aortic aneurysm, or both. In this position, the heart serves as a window through which the ultrasound beam can be passed to visualize the lower portion of the descending thoracic aorta. Since lung is not present between the chest wall and the aorta at this level, it is not surprising that the aorta can easily be visualized in most patients. Improved visualization with the more leftward transducer position likely reflects the fact that the aorta descends within the left chest. The ability, using this transducer position, to visualize the aorta changing from its short to long axis during 90° rotation of the transducer will also permit differentiation of the aorta from other structures, such as the coronary sinus, which may also be visualized in short axis posterior to the cardiac chambers.

Use of the modified left parasternal technique appears sensitive in identifying abnormalities of the de-

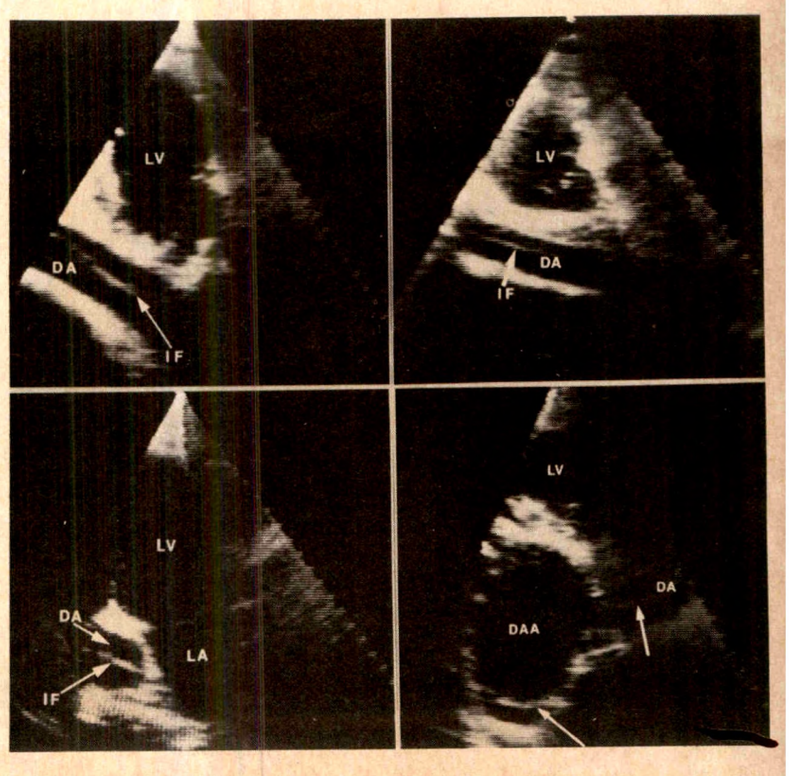

FIGURE 2. Cross-sectional echocardiographic findings in patients with abnormalities of the retrocardiac descending aorta. **Top left,** in Patient 1, an intimal flap (IF) was visualized within the enlarged descending thoracic aorta (DA), which measured 2.9 cm in diameter. **Top right,** an oscillating intimal flap (IF) was visualized within the descending thoracic aorta (DA) of Patient 2. The diameter of the aorta measured only 2.2 cm in this region. **Bottom left,** in short axis the descending thoracic aorta (DA) in Patient 3 demonstrates the intimal flap (IF) which was seen to oscillate reproducibly during systole and diastole. **Bottom right,** in Patient 5, a large saccular descending aortic aneurysm (DAA) is seen to arise from a normal caliber upper descending aorta (DA), which measured 2.2 cm in diameter. The saccular aneurysm measured over 8 cm in diameter. Internal echoes (**white arrows**) within the DA and DAA may have represented intimal flaps suspected on computerized tomography. LA = left atrium; LV = left ventricle. One centimeter markings are displayed on the right side of the sectors.

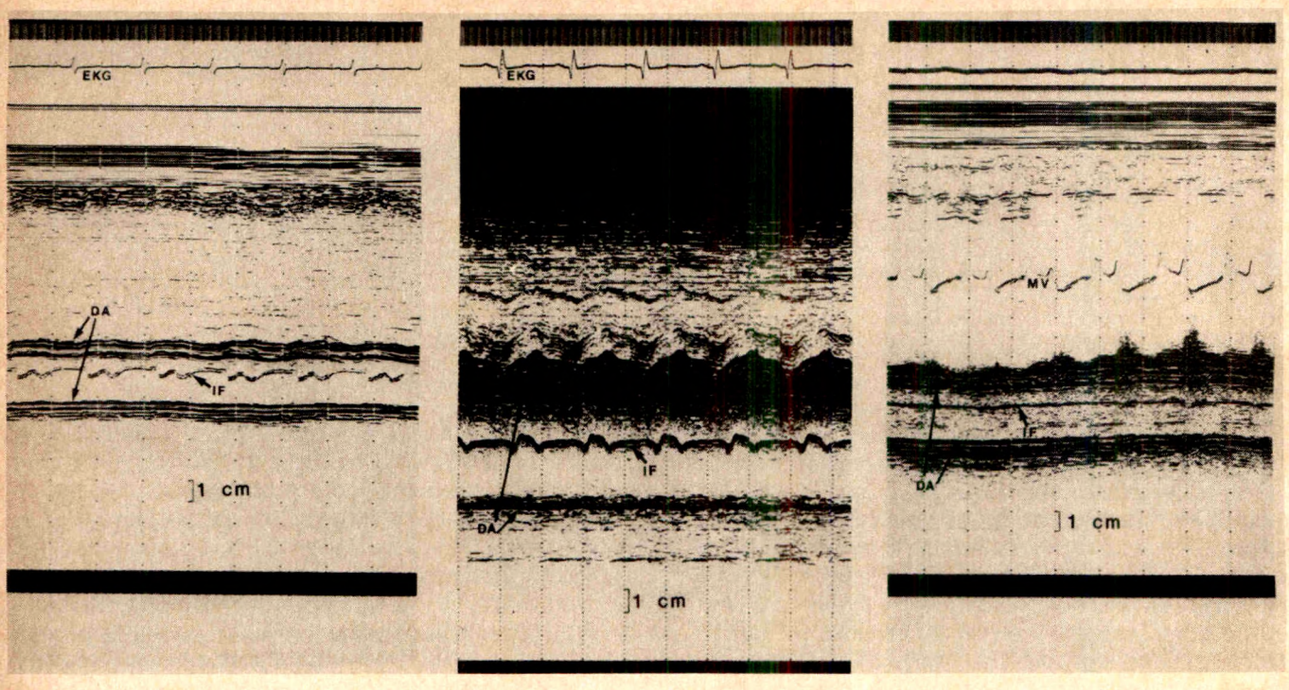

FIGURE 3. M-mode echocardiograms of the descending thoracic aorta (DA) were obtained using the M-mode cursor of the cross-sectional echocardiograph. The internal echoes, almost certainly representing intimal flaps (IF), are seen to have an oscillating pattern of movement in systole and diastole in Patients 2 and 3 (**left and middle**). The movement of the flap is seen to be different from the movement of the aortic walls, presumably reflecting differential rates of filling of the true and false lumens. The aortic walls appear thickened in Patient 2, possibly as a result of a subintimal hematoma. In Patient 4 (**right**), the internal echo is separated from the anterior aortic wall by approximately 1 cm but is nonmoving. EKG = electrocardiogram; MV = mitral valve.

scending aorta when they extend to the retrocardiac region. This technique demonstrated abnormalities in all 5 patients confirmed to have aneurysmal dilatation or aortic dissection, or both, on aortogram or on computerized tomography. With combined echocardiographic examination of the ascending and descending thoracic aorta, all patients with dissection were accurately classified by echocardiographic study as having either DeBakey type 1 or 3 dissections, as compared with results of aortograms, surgical observations, and computerized tomography.

The abnormalities identified, including appreciable dilatation of the aorta and abnormal internal echoes, appear to be quite specific for aortic pathology. Linear stationary or oscillating echoes were not visualized between the anterior and the posterior walls of the aorta in any of the 50 consecutive patients. While not recognized in our control patients, the possibility of false-positive findings in studies for dissection certainly exist. For example, in a patient with excessive thickening of the aortic walls, it is possible that the intima might be visualized as widely separated from the outer wall. In addition, lateral spread of the sound beam in the far field or reverberations could potentially cause the appearance of spurious echoes within the aorta. To diminish the possibility of a false-positive finding, the abnormality should optimally be visualized in short as well as long axis, and reverberations from anteriorly positioned structures should be excluded. Oscillation of an apparent intimal flap during systole and diastole may enable a more specific diagnosis of dissection, since it suggests the presence of true and false lumens, with differential time courses of filling (Fig. 3).

Larger studies are necessary to define further the sensitivity and specificity of echocardiographic techniques in the recognition of all types of aortic pathology. However, this and other previous cross-sectional echocardiographic studies[3–8] suggest that ultrasonic techniques may indeed prove useful in the initial evaluation of patients presenting with symptoms or signs, or both, suggestive of acute or chronic aortic pathology.

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Respiratory Effects on Systolic Time Intervals During Pericardial Effusion

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Pericardial effusion without cardiac tamponade is defined by the detection of excessive pericardial fluid without clinical manifestations, particularly pulsus paradoxus (inspiratory decrease in systolic blood pressure >10 mm Hg) and jugular venous distention. Nineteen consecutive patients without heart or lung disease who had pericardial findings and no evidence of tamponade were investigated by echocardiography: 14 with pericardial effusion and 5 with noneffusive ("dry") pericarditis. Patients with effusion had an inspiratory decrease in left ventricular ejection time (ΔLVET) of 17.9 ± 5.78 ms and an increase in preejection period (ΔPEP) of 12.1 ± 3.78 ms, each well beyond the respective respiratory changes measured in normal subjects. The 5 control patients with dry pericarditis had a mean ΔLVET and ΔPEP of only 8.0 and 7.0 ms, respectively. Of the 14 patients with effusion, 6 whose systolic pressure showed no respiratory change had mean ΔLVET of 13.7 ms and ΔPEP of 11.2 ms, comparable to the other 8 patients with effusion who had a respiratory change of 2 to 10 mm Hg. We conclude that although pulsus paradoxus was not present, excessive pericardial fluid is not physiologically inert. If a satisfactory echocardiogram is not available, exaggerated respiratory fluctuation in systolic time intervals may be evidence of excessive pericardial fluid.

Exaggerated inspiratory reduction in left ventricular function, clinically expressed as pulsus paradoxus (defined as a >10 mm Hg inspiratory decrease in systolic blood pressure during quiet breathing[1]), is a hallmark of cardiac tamponade. In contrast, most pericardial effusions are not accompanied by clinical signs of abnormal cardiac function, including pulsus paradoxus, and so long as an effusion does not significantly compress the heart, invasive measurements are not justified. Indeed, repetitive search at the bedside for pulsus paradoxus is the common means of monitoring effusions for the development of cardiac tamponade. Two reports[2,3] mention 3 patients with pericardial effusion but no tamponade who had marked respiratory changes in left ventricular ejection time of 25 to 50 ms without pulsus paradoxus. These were 3.5 to 7 times the expected mean respiratory change in left ventricular ejection time (LVET) (7.1 ± 2.3 ms) observed in normal subjects and in patients with stable coronary disease.[4,5] Moreover, Carter et al[2] could only induce up to a 10 ms change in ejection time even with "accentuated respiration" in 10 patients free from pericardial fluid.

A greatly exaggerated respiratory change in ejection time due only to the presence of pericardial fluid could have important physiologic, and perhaps diagnostic, implications. Moreover, the effect on the other major systolic time interval (STI), the preejection period (PEP), has not been reported. Because a predictable effect on STI would indicate that in the absence of tamponade, pericardial fluid is not physiologically inert, we wished to determine (1) whether PEP was also affected by nontamponading pericardial fluid, (2) how often the STIs were significantly affected, and (3) the relation of such effects to effusion size.

We studied prospectively the STI in 20 consecutive patients with pericardial disease but without cardiac or pulmonary disease and with a normal, regular breathing pattern demonstrated by thermistor recordings. These included (1) 15 consecutive patients with pericardial effusion who had no signs of cardiac or pulmonary embarrassment, no pulsus paradoxus, and no jugular venous distention, and (2) 5 patients with noneffusive (dry) pericarditis, that is, with absolutely no evidence of pericardial fluid on echocardiogram. (We recognize that >10 mm Hg may be arbitrary for pulsus paradoxus, but it is the generally accepted cutoff.[1])

Methods

Study patients: All patients presenting at the echocardiographic laboratory were screened for pericardial effusion. One patient was excluded after recording because of sinus arrhythmia. Fourteen consecutive patients with detectable pericardial fluid were identified with the following characteristics: (1) pericardial effusion without echocardiographic signs associated with cardiac tamponade,[6] (2) respiratory variation of ≤10 mm Hg in brachial artery systolic pressure (measured by cuff in the echocardiography laboratory), (3) no jugular venous distention, (4) electrocardiogram showing

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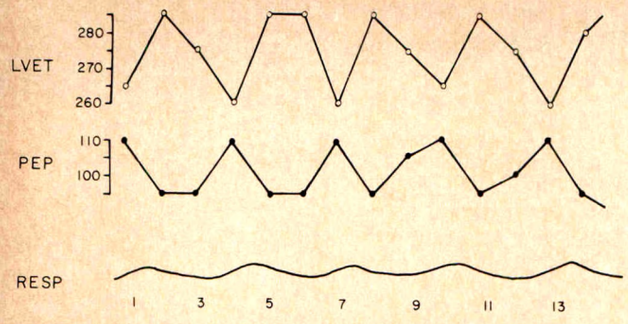

FIGURE 1. Beat-to-beat fluctuation in left ventricular ejection time (LVET) and preejection period (PEP) in a 67-year-old woman with rheumatoid arthritis and moderate-sized pericardial effusion. RESP = thermistor tracing, inspiration upward. Minimal LVET and maximal PEP occur very close to peak inspiration.

stable sinus rhythm without significant respiratory changes, (5) absence of respiratory disease or disordered breathing patterns and subsequently a clear second heart sound in phonocardiograms. Graphic recordings were made on an Irex System II recorder using Leatham suction microphones with filter adjustments to record optimal second heart sounds.

Study protocol: Immediately after echocardiography established the presence of pericardial effusion, patients were investigated by recording at a paper speed of 100 mm/s: (1) phonocardiogram at a position to clearly register the aortic component of the second heart sound (usually left midsternal border), (2) right carotid displacement pulse, and (3) phasic breathing changes through a thermistor sensor. The preejection period and left ventricular ejection time were measured in milliseconds in continuous respiratory cycles with technically good waveforms. The timing of II_A (q − II_A) was taken as electromechanical systole (EMS). Left ventricular ejection time was calculated by subtracting q − CARu from q − CAR_{In}. The PEP was obtained by subtracting LVET from EMS: that is, PEP = EMS − LVET.[7]

To minimize bias, measurements were made without reference to the respiratory trace. Heart rates were measured by cycle-to-cycle measurements of R-R intervals in milliseconds and expressed as beats per minute. After all measurements were completed, the respiratory tracing was correlated and minimal and maximal ejection and PEPs (expressed to the nearest 5 ms) were determined for each patient for each respiratory cycle.

TABLE I Respiratory Change

Effusion: Echocardiographic Estimate	n	Mean ΔPEP (ms)	Mean ΔLVET (ms)	Range ΔSyst BP (mm Hg)
Minimal to small	3	10.0	11.7	0–10
Moderate	5	12.0	22.0	0–10
Moderately large to large	6	13.7	17.5	0–8
Total (mean ± SD)	14	12.3 ± 3.78	17.9 ± 5.78	0–10
Controls (dry pericarditis)	5	7.0 ± 2.73	8.0 ± 2.73	0–4
Effusion patients with ΔSyst BP = 0	6	11.2	13.7	0

ΔLVET = inspiratory decrease in left ventricular ejection time; ΔPEP = increase in preejection period; ΔSyst BP = change in systolic blood pressure; SD = standard deviation.

A separate observer, with no knowledge of any other findings, evaluated the echocardiograms without reference to the other findings to estimate the amount of pericardial fluid[6] in the following ranges: minimal, small, moderate, moderately large, and large. The following criteria were used: *minimal:* all fluid posterior and appearing only during systole or systole and early diastole; *small:* all fluid posterior, appearing throughout systole and diastole and <10 mm deep; *moderate:* all fluid posterior with wide (≥10 mm) separation of epicardium from parietal pericardium with or without a trace of fluid anteriorly; *moderately large:* posterior fluid plus up to 5 mm anterior fluid; and *large:* posterior fluid plus anterior fluid ≥10 mm. More quantitative estimation was avoided because of serious inaccuracies using M-mode echocardiography.[6]

Patients with dry pericarditis were identified by a typical pericardial rub with typical or atypical[8] electrocardiographic changes, in the presence of a syndrome consistent with acute pericarditis, and by echocardiograms showing no fluid. The foregoing procedure for STI and respiratory tracings was followed.

Results

Fourteen consecutive patients with pericardial effusion and 5 consecutive patients with dry pericarditis were investigated. The same directional changes occurred in every patient: maximal preejection period and minimal ejection time always occurred in beats at or closest to peak inspiration (Fig. 1). Heart rates ranged between 64 and 122 (mean 91.5 beats/min). Heart rate change during respiration was minimal, making it unnecessary to rate-index the ejection time.

Results are summarized in Table I. By protocol, no patient had a respiratory change in blood pressure of >10 mm Hg. In fact, only 2 patients had a 10 mm Hg decrease in systolic blood pressure; 4 had a 6 mm Hg decrease and 1 each had 7 and 8 mm Hg inspiratory decreases in systolic pressure. Six had no detectable respiratory change. Because of the small numbers, the individual judgments of effusion size were consolidated in 3 final categories, resulting in 3 patients with minimal to small effusions, 5 with moderate effusion, and 6 with moderately large to large effusions.

Table I shows a mean inspiratory increase in the preejection period (ΔPEP) of 12.3 ms with a small standard deviation and very little difference according to size of the effusion. The mean inspiratory decrease in left ventricular ejection time (ΔLVET) was larger, being 17.9 ± 5.78 ms. The largest mean ΔLVET was in moderate sized effusions, of 22.0 ms; the smallest ΔLVET was in the minimal to small group (11.7 ms). (Because of the relatively small size of each subgroup, statistical tests were not applied to subgroup differences.) In contrast, patients with dry pericarditis had mean changes in left ventricular ejection time of 8.0 ms and in the preejection period of 7.0 ms.

Discussion

Normal ambulatory subjects and stable coronary patients without pericardial disease have very small respiratory changes in left ventricular ejection time (mean ± standard deviation [SD] 7.1 ± 2.3) and in the preejection period (mean 4.2 ± 3.3 ms), respectively.[4,5] In the absence of pericardial fluid, even "accentuated

breathing" could only induce LVET changes up to 10 ms.[2] With nontamponading pericardial effusion, respiratory changes in each of these measurements clearly tend to be greater despite the absence of pulsus paradoxus. (Indeed, separate measurements in the 6 patients with no detectable respiratory change in systolic blood pressure [Table I] showed that ejection and preejection period changes were entirely comparable to those of the whole group: mean ΔLVET 13.7 ms; mean ΔPEP 11.2 ms.) It is also clear that the mean changes were greater than those in the 5 control patients with dry pericarditis, who had respiratory changes in ejection time comparable to those of the normal subjects and coronary patients previously reported.[4,5]

Because hemodynamic measurements were not made in these patients, mechanism-related explanations of the results necessarily remain speculative, although consonant with known physiologic events. The directional changes in the preejection period and left ventricular ejection time were those expected in response to reduced volume load (and, hence, preload) in the left ventricle. Because LVET is nearly always 2.5 to 3.5 times the duration of the preejection period, and the mean respiratory change in ejection time only about 1.5 times that of the preejection period, the relative change in the preejection period is much larger than that in the ejection time. These disproportionate changes are not surprising because a relatively greater change in preejection period is characteristic of many conditions with beat-to-beat changes in left ventricular filling such as atrial fibrillation, varying atrioventricular block, ectopic beats, and postectopic augmented beats.[9]

The findings in this investigation have several implications which ethically could only be studied noninvasively because "innocent" pericardial fluid made invasive procedures, such as pericardiocentesis, and vascular or cardiac catheterization unjustifiable in these patients. (In none did tamponade subsequently develop.) Yet, the changes indicate that the presence of apparently noncompressing pericardial effusion does not mean that the fluid lacks influence on cardiovascular physiology. The fact that cuff blood pressure could not identify pulsus paradoxus within the common definition of that term (indeed, 6 patients with no change in blood pressure had LVET and PEP changes comparable to those of the whole group) does not mean that the fluid was inert or even that its pressure was nil. Depending on the elasticity of the parietal pericardium, a critical but individually variable amount of fluid could cause intrapericardial pressure to increase slightly but significantly during inspiration. Normally and also during pericardial effusion and tamponade, pericardial pressure decreases during inspiration, paralleling pleural pressure. This accelerates caval blood flow into the right heart, and the right ventricle expands producing a secondary increase in pericardial pressure. During tamponade, that expansion increases inspiratory compression of the left ventricle, producing a greater than normal decrease in left ventricular input and, hence, output—pulsus paradoxus. Indeed, during experimental tamponade, if inspiratory right heart filling is prevented, pulsus paradoxus is absent.[1] Our patients' clinically noncompressing pericardial effusions may represent an intermediate state in which comparable mechanics occur to a lesser degree and affect other, perhaps more sensitive, expressions of function, that is, the STI. (Our patients also did not have the gross septal shift seen with pulsus paradoxus.) Group differences based on effusion size alone may not show smooth gradations because of an unmeasurable element: interpatient variability in stiffness of the parietal pericardium, including changes related to duration and rate of accumulation of effusion (unknown quantities). Thus, in Table I, ΔLVET was greater for moderate than for large effusions, perhaps for this reason.

Simultaneously decreasing LVET and increasing PEP are characteristic effects of decreasing preload.[3,9] Exaggeration of corresponding expected respiratory changes in LVET and PEP are most consistent with greater than normal inspiratory decrease in left heart filling,[1] that is, preload. Indeed, Janicki et al[10] recently showed that the filling gradient between pulmonary veins and left ventricle is especially sensitive to the presence of pericardial fluid over a wide range of pericardial pressures from −3 to +20 mm Hg, implying responses at quite low levels of intrapericardial pressure change. Excessive respiratory changes in STI with nontamponading effusions are consistent with these observations. Moreover, because such changes were not present with "dry" pericarditis, this implies that (1) irrespective of whether our patients' effusions did not compress the heart, invasive procedures not being indicated, the fluid was not physiologically inert; (2) abnormal respiratory changes in blood pressure, at least by cuff, may be less sensitive than STI to the physiologic effects of nontamponading fluid; (3) in the absence of satisfactory echocardiographic tracings, the degree of respiratory fluctuation in STI may provide evidence for or against excessive pericardial fluid as a component of an enlarged cardiac silhouette.

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Usefulness of Echocardiographic Right Ventricular Measurements in Estimating Right Ventricular Hypertrophy And Right Ventricular Systolic Pressure

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Right ventricular wall thickness (T) measurements were made in 111 patients by echocardiography to evaluate their usefulness in diagnosing right ventricular hypertrophy (RVH) and in predicting right ventricular peak systolic pressure (P). Anatomic and echocardiographic findings of RVH were compared in 36 of 111 subjects: diastolic T (dT) and systolic T (sT) had a sensitivity of 90 and 34% and a specificity of 94 and 100%, respectively, in the diagnosis of RVH. Echocardiographic and hemodynamic findings were compared in the remaining 75 of 111 patients undergoing cardiac catheterization: dT was 6.5 ± 2.7 mm in 46 patients with elevated P (58.2 ± 30.2 mm Hg) versus 3.8 ± 0.9 in 29 patients with normal P (26.3 ± 2.7 mm Hg) ($p < 0.01$). The dT and P had a linear correlation ($r = 0.92$) in 40 patients with right ventricular end-diastolic dimension <13 mm/m^2. Estimates of P in 22 patients with atrial septal defect and right ventricular end-diastolic dimension >13 mm/m^2 were fairly good ($r = 0.83$). It is concluded that echocardiographic measurements of T are useful in diagnosing RVH and in estimating P.

Echocardiographic measurements of right ventricular wall thickness (T) were first made and reported in children.[1–3] Recently, echocardiographic recordings of the right ventricular wall were obtained by several investigators by the subxiphoid and anterior parasternal techniques[5–12] in adult patients with congenital heart disease,[3,4] in athletes,[5] in patients with amyloid cardiomyopathy,[6] in normal subjects,[7] and in patients with myocardial infarction.[8] Furthermore, measurements of diastolic T(dT) have also been useful in the diagnosis of right ventricular hypertrophy (RVH) in adults.[9] In this report we attempt to answer the following questions: Are the echocardiographic measurements of T useful in the diagnosis of RVH? Does a good correlation exist between the echocardiographic T and the right ventricular peak systolic pressure (P)? Can P be predicted from measurements of T?

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Methods

A total of 111 subjects aged 12 to 87 years were studied. The patient population included 23 patients with coronary heart disease, 22 with atrial septal defect, 20 with mitral valvular disease, 12 with combined mitral and aortic valvular disease, 11 with cardiomyopathy, 5 with hypertension, 3 normal subjects, 3 with aortic valve disease, 2 with chronic obstructive pulmonary disease, 2 with pentalogy of Fallot, 1 with tetralogy of Fallot, 4 with pulmonary stenosis, 1 with primary pulmonary hypertension, and 2 with ventricular septal defect. Necropsy measurements of T were made in 36 of the 111 patients who died within 1 month of the echocardiographic study. The remaining 75 patients underwent right heart catheterization.

Echocardiographic technique: *Anterior parasternal approach:* Echocardiograms were recorded on a strip chart recorder (Smith Kline Instruments, Toshiba Sonolayergraph model SSH 10A, or Aloka SSD-90 recorders) in M-mode using a 2.25 MHz transducer from the left fourth intercostal space in supine position. It was necessary to carefully adjust the near gain, coarse gain, and depth compensation controls to record a clear right ventricular wall.[10] The T was measured in a plane where the interventricular septum and the posterior left ventricular wall were seen below the level of the mitral valve. The right ventricular end-diastolic dimension (D) and the dT were measured at the beginning of the QRS on the electrocardiogram and the systolic right ventricular wall thickness (sT) was measured where the thickness of the right ventricular wall was at its greatest (Fig. 1). The right ventricular wall

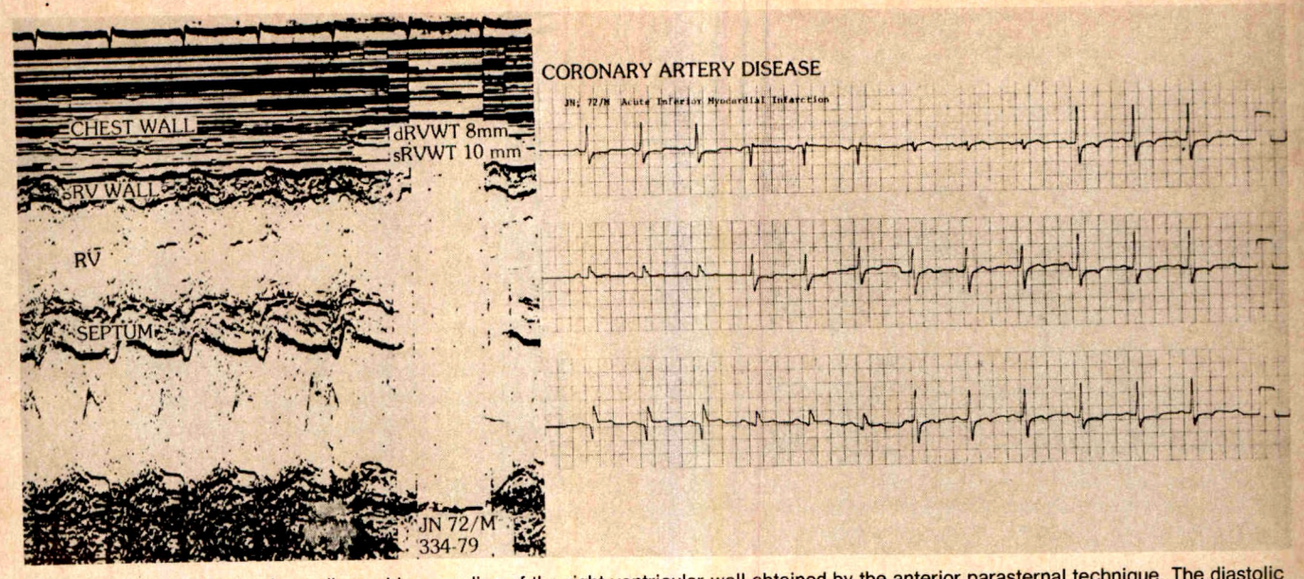

FIGURE 1. An untouched echocardiographic recording of the right ventricular wall obtained by the anterior parasternal technique. The diastolic (dRVWT) and systolic right ventricular wall thickness (sRVWT) in this echocardiogram are 8 and 10 mm, respectively, and meet the echocardiographic criteria for the diagnosis of RVH. The right ventricular end-diastolic dimension is also abnormal and measures 33 mm. This 72-year-old man had had an acute anterior wall myocardial infarction and manifested right ventricular failure. The diagnosis of RVH is not clear-cut in this 12-lead electrocardiogram.[10,18] Two subtle signs suggestive of RVH are present: (1) S_1,Q_3 (sensitivity 25% and specificity 87%), and (2) SV_5 and SV_6 (sensitivity 58% and specificity 53%).[18]

echoes move away from the transducer during systole. Five beats were separately measured to obtain an average T. The T is the distance between the epicardium and the endocardium of the right ventricular wall and the measurements were made by the leading edge method. The echoes were not read blindly, and the clinical diagnosis was known in most cases. At the same preselected location, T was measured by 2 observers in 25 patients; the difference in the measurements of the T was ≤1 mm. Measurements of T by the same individual on 2 different occasions showed a variation of 0.1 to 0.3 mm in 25 patients. Each 1 cm mark on the echocardiographic tracing was divided into 10 or more equal parts to increase the accuracy of the measurements. The final reported measurement was rounded to the closest millimeter. All tracings were made during normal quiet breathing.

Subxiphoid approach: The transducer was placed on the subxiphoid area and directed posteriorly, superiorly, and to the left.[11] With the septum as a landmark, the orientation of the transducer was adjusted to obtain excellent visualization of the right ventricular wall. Echoes from the chordae tendineae attaching to the tricuspid leaflets were frequently visualized; they can easily be misidentified as the endocardium. This can be avoided by the use of contrast method during an M-mode scan. Figure 2 shows that echoes produced by contrast dye are demonstrated not to enter between 2 parallel echoes identified as the right ventricular wall, thus proving a definite visualization of the endocardium.

Right heart catheterization: Seventy-five subjects underwent diagnostic right heart catheterization within 1 week of the echocardiographic examinations. In this study the patients were considered to have right ventricular pressure overload when the P was ≥31 mm Hg. T was measured by the subxiphoid as well as the anterior approach in these patients.

Necropsy technique: At necropsy, the hearts were dissected in a uniform manner and the T measurements were made without knowledge of the echocardiographic measurements. T was measured in millimeters with a ruler, in the midportion of the free wall of the right ventricle (between the base and the apex).[12] Sections were carefully made to avoid the valleys between the trabeculations. The normal T at necropsy is 2 mm, and RVH is present when the T is ≥5 mm.[13–16] Thus, a 5 mm thick right ventricular wall at necropsy was considered diagnostic of RVH.[9,13–16] Twenty patients had no RVH as T at necropsy was ≤4 mm, and 16 patients had RVH as T was ≥5 mm at necropsy.

Statistical analysis was performed using standard least-squares linear regression analysis and Student's *t* test.

Results

Echocardiographic and necropsy correlation: The echocardiographic dT was 3.3 ± 0.6 mm (range 2 to 4) in patients with no RVH versus 5.9 ± 0.9 mm (range 5 to 8) in RVH patients ($p < 0.01$): dT ≥5 mm had a sensitivity of 90% and a specificity of 94% in diagnosing RVH. The sT was 5.1 ± 1.5 mm in patients with no RVH versus 9.1 ± 2.9 mm in patients with RVH ($p < 0.01$): sT ≥10 mm had a sensitivity of 34% and a specificity of 100% in diagnosing RVH.

Echocardiographic and hemodynamic correlation: Of the 75 patients undergoing right heart catheterization, 29 did not have right ventricular pressure overload (mean P 26.3 ± 2.7 mm Hg) and 46 patients had right ventricular pressure overload (mean P 58.2 ± 30.2 mm Hg) ($p < 0.01$). T was 3.8 ± 0.9 mm in patients without and 6.5 ± 2.7 mm in patients with right ventricular pressure overload ($p < 0.01$) (Fig. 3). P was ≤30 mm Hg in 23 of 30 patients with dT of 2 to 4 mm and was increased in all 11 subjects with dT ≥8 mm. P was 43, 74, and 91 mm Hg in 3 patients with dT of 8 mm; 84 and 110 mm Hg in 2 patients with dT of 9 mm; and 100,

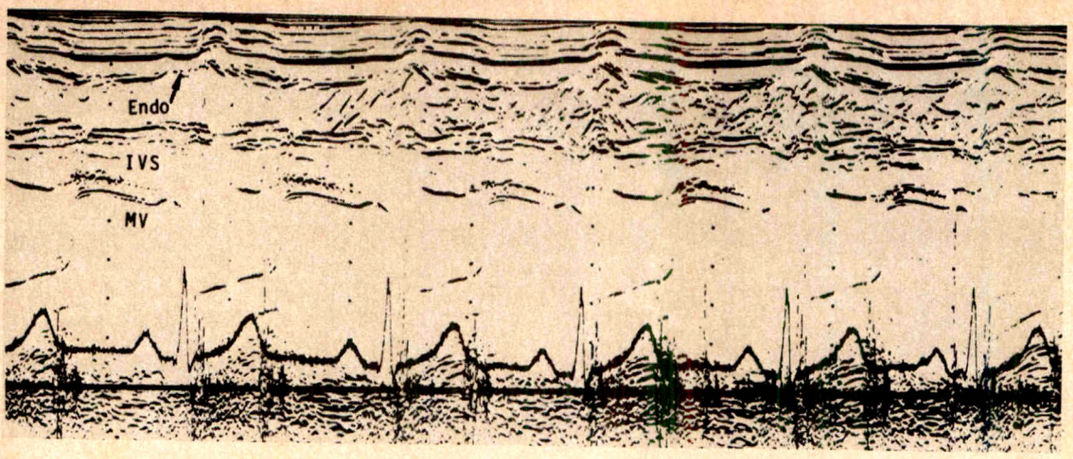

FIGURE 2. Contrast method for identification of the endocardium (Endo). The echoes produced by the contrast medium are seen in the right ventricular cavity and do not enter the space between the 2 parallel echoes of the right ventricular wall representing the endocardium (directly in contact with the contrast) and the epicardium. IVS = interventricular septum; MV = mitral valve.

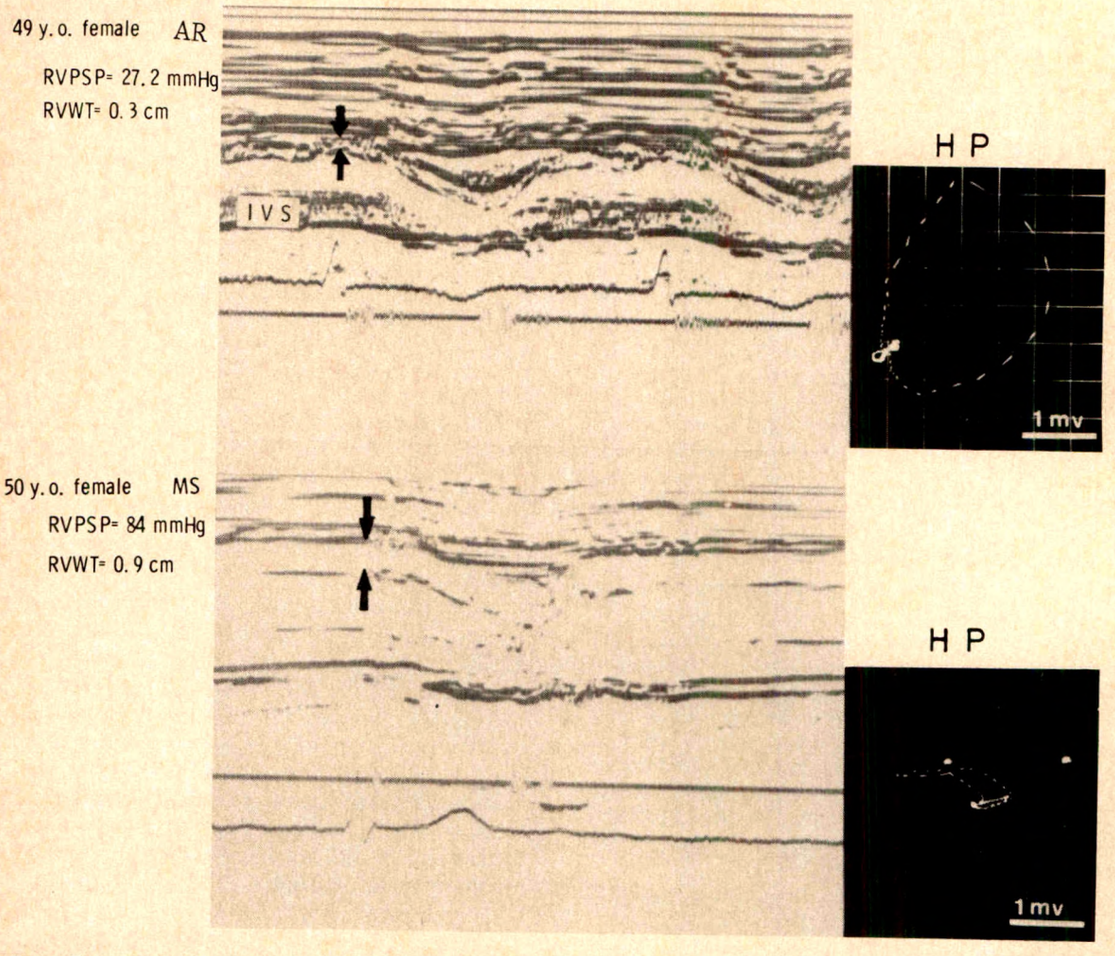

FIGURE 3. Recordings of the right ventricular wall obtained in 2 patients are shown along with their vectorcardiograms. The **upper panel** shows that the diastolic right ventricular wall thickness (RVWT) measured 3 mm in this 49-year-old woman with aortic regurgitation (AR). Right ventricular peak systolic pressure (RVPSP) was 27.2 mm Hg and the vectorcardiogram shows left ventricular hypertrophy. In the **lower panel** the RVWT is 9 mm. There is also evidence of RVH (type C) on the vectorcardiogram in this 50-year-old woman with mitral stenosis (MS). RVPSP was 84 mm Hg. HP = horizontal plane of the vectorcardiogram; IVS = interventricular septum.

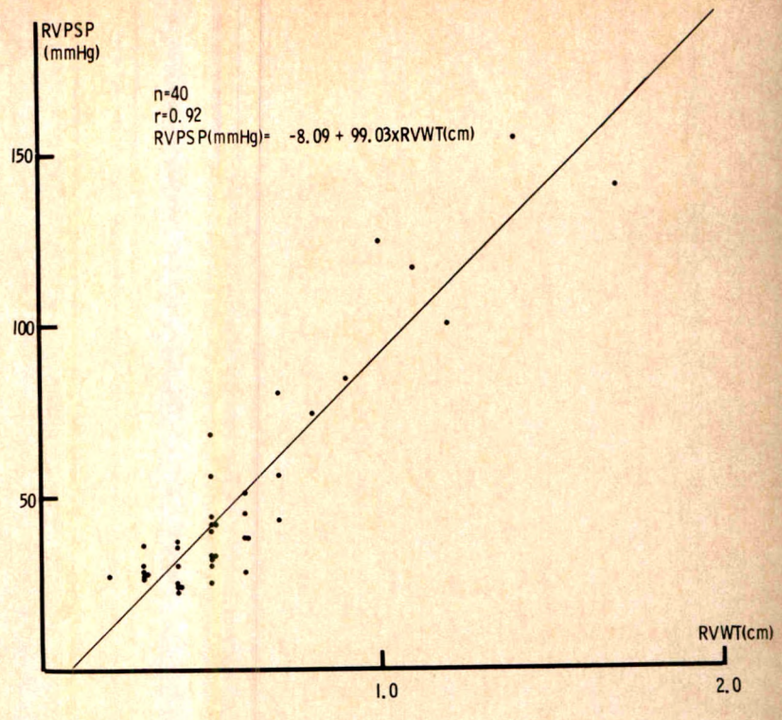

FIGURE 4. Correlation between the right ventricular peak systolic pressure (RVPSP) and the diastolic right ventricular wall thickness (RVWT) measured by echocardiography is shown in 40 patients with a right ventricular end-diastolic dimension index ≤ 12 mm/m^2 and was good ($r = 0.92$). The following regression equation was obtained: RVPSP (mm Hg) = $-8.09 + 99.03 \times$ T (cm).

124, 116, 140, 154, and 82 mm Hg in 6 patients with dT $\geq$10 mm. Measurements of T were correlated with P, and the correlation coefficient (r value) for the 75 patients was 0.89.

The role of D was then examined in relation to T and P. The 75 patients were divided into 2 groups on the basis of D $\geq$13 mm/m^2. Forty patients had D <13 mm/m^2 (mean 8.7 $\pm$ 2.2 mm/m^2), and 35 patients had a dilated right ventricle with a mean D of 19.5 $\pm$ 5.8 mm/m^2. As might be expected, all 22 patients with atrial septal defect had a dilated right ventricle (D $\geq$13 mm/m^2). Measurements of T were found to have a good linear correlation with P ($r = 0.92$) in patients with D <13 mm/m^2 (Fig. 4). The following regression equation was obtained: P (mm Hg) = $-8.09 + 99.03 \times$ T (cm). The standard error of the pressure estimates (SEE) was 13.2 mm Hg. Using this equation, we tried to predict P in 35 patients with D $\geq$13 mm/m^2. In 22 patients with atrial septal defect, the slope of the regression between the predicted and measured P was 1.03, with a correlation coefficient of 0.83. Only 1 patient with atrial septal defect fell out of the 1 SEE. However, of the remaining 13 of 35 subjects with D $\geq$13 mm/m^2 and no atrial septal defect, 5 fell out of the 1 SEE, although only 1 of the 2 SEE (Fig. 5).

Discussion

As echocardiographic measurements of T are useful in diagnosing RVH and predicting P, it is important to examine the feasibility of the echocardiographic technique for obtaining right ventricular wall recordings. High quality echocardiographic tracings were obtained in 90% of infants and children up to 18 years of age by Arcilla and associates.[3] A yield of over 80% has been reported with the anterior parasternal approach[7,9,10,12] and over 90% with the subxiphoid technique in adults.[11] The best way to record the right ventricular wall by echocardiography was prospectively investigated in 40 consecutive adult subjects (normal subjects and patients with congenital and acquired cardiac disease) by Tsuda et al.[7] The highest successful recording rate was 80% and was achieved by an anterior approach from the left sternal border in the supine position: the yield with the subxiphoid approach was 50%.[7] These studies confirm our experience that it is feasible to obtain echocardiographic right ventricular wall recordings in adults.

In the present study, the dT measured 3.8 $\pm$ 0.9 mm in cardiac patients without right ventricular pressure overload, 3.3 $\pm$ 0.6 mm in patients with no RVH at necropsy, 6.5 $\pm$ 2.7 mm in patients with right ventricular pressure overload, and 5.9 $\pm$ 0.9 mm in patients with RVH at necropsy. The mean dT in normal subjects was 2.4 $\pm$ 0.5 mm in the study of Tsuda et al[7] using the anterior approach and 3.4 $\pm$ 0.8 in the study of Matsukubo et al[11] using subxiphoid approach. RVH as indicated by an increased dT has also been found in patients with right ventricular volume and pressure overload, in male and female long-distance runners,[5] and in patients with amyloid cardiomyopathy.[6] The dT and sT had a sensitivity of 90 and 34% and a specificity of 94 and 100%, respectively, for diagnosing RVH.

The correlation coefficient (r value) between dT and P in all 75 patients was 0.89, but improved to 0.92 when correlation between dT and P was determined only in the 40 patients with D <13 mm/m^2. P could be predicted accurately in all patients with D <13 mm/m^2 as

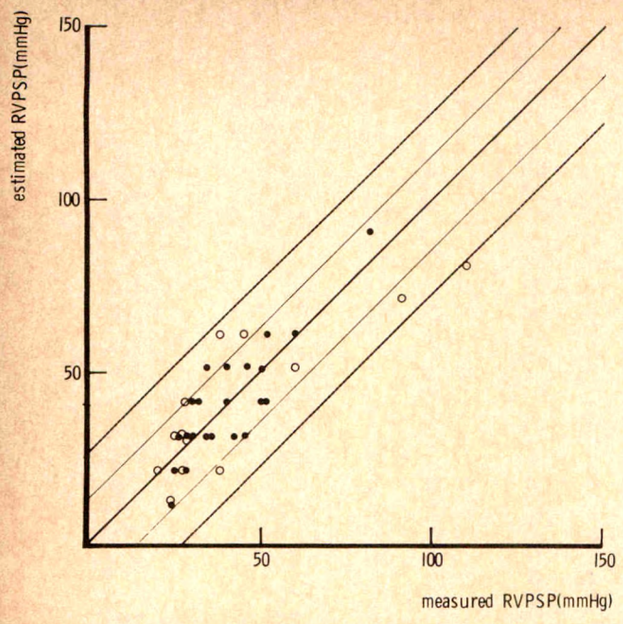

FIGURE 5. Correlation between the measured right ventricular peak systolic pressure (RVPSP) and the estimated values of P calculated from the regression equation. **Closed circles** denote patients with atrial septal defect and **open circles** denote the remaining subjects with DI >1.3 cm/m^2. A fair correlation is seen in patients with atrial septal defect, the slope of the regression between the predicted and measured P was 1.03, the correlation coefficient was 0.83, and only 1 patient fell out of line representing 1 SEE. In the remaining 13 patients, P was not accurately predicted.

well as in patients with atrial septal defect with D >13 mm/m^2. However, in the remaining 13 patients with no atrial septal defect and D >13 mm/m^2, P could not be accurately predicted, possibly for the following reasons: (1) The value of P was overestimated in a 50-year-old woman who underwent mitral commissurotomy 16 months before the present investigation. Overestimation may have been due to failure of the RVH to regress postoperatively; P was 65 mm Hg before operation and 37 mm Hg during the current study. (2) By combined use of the subxiphoid 2-dimensional and M-mode techniques, we confirmed that the echocardiographic beam normally passes through the midportion of the free wall of the right ventricular inflow tract and the degree of RVH is uniform in most cases of atrial septal defect. However, the degree of RVH differed from the base to the apex of the right ventricular inflow tract in 2 patients, 1 with tetralogy of Fallot and the other with primary pulmonary hypertension. Therefore, a change in the angulation of the transducer may result in an error in the estimation of the true thickness of the right ventricular wall when RVH is not uniform. (3) Moreover, the pulmonary arterial systolic pressure can change in some patients with right ventricular pressure overload because of changes in heart rate, respiration, and ventricular contractility, as was observed by us in 1 patient (34-year-old woman) with mitral stenosis and regurgitation.

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LETTERS*

BLIND REVIEWS

This letter offers a brief comment on your recent statements concerning blind reviews. Although the motivation for impartiality in reviewing scientific manuscripts is well understood, my experience as both an author and a reviewer supports the side of nonblind reviews. The weight of my opinion rests on one crucial point. As an author, it is important to me to make clear to the reader which aspects of my results or my discussion are based on previous work in my or my colleagues' laboratories. I generally attempt to clearly identify for the reader those parts of the discussion that refer to work performed in our institution. The reader needs to clearly understand how much of the case being made has been built up in one environment and how much derives its foundation from various institutions. It is unfair to deny a reviewer that information.

Typically, a reviewer would appreciate a clear understanding of the extent of the author's background in the area being investigated and whether methods used or conclusions drawn are founded in well-experienced laboratories. In addition, little effort is required by the reviewer to determine the source of an article even in a blind review. Unfortunately, some reviewers are unfairly prejudiced against a particular investigator or investigators. However, individuals who apply such partialities will go to the necessary effort to identify the source of a given article. Normally, a brief review of the reference list will clearly identify the source. Therefore, blind reviews will generally not prevent such prejudicial refereeing.

The position of editor is a difficult one. For my own work, I will submit my articles clearly identified with their source and will request nonblind reviews. I will also urge my colleagues to do the same. Time will prove that the only means to prevent prejudiced reviews is to clearly document them and to eliminate those reviewers from your list. Your open approach to this problem and the editorial policy that allows contributing authors to choose the manner in which their particular manuscript is reviewed is greatly appreciated.

Michael D. Devous, Sr., MD
Dallas, Texas

I read of your intention to initiate blind reviews for manuscripts submitted to your *Journal*. I think this is an excellent idea which not only may offer a greater equity with respect to acceptance of papers but also may allow the opportunity to determine whether reviewer bias exists.

If possible, it would be important to submit each manuscript for both a "blind" and a "standard" review. An additional step would be to have 2 "standard" reviewers: 1 prominent in the field addressed by the author, the other with competence in another area of cardiology. I realize that the review process, at best, is somewhat subjective, requiring a large number of reviewers to be involved before a meaningful conclusion is reached concerning reviewer bias. However, the volume of manuscripts submitted to the *Journal* could provide for sufficient numbers if the extra work would not be a great burden.

Barry Stimmel, MD
New York, New York

Since you asked for comments on this issue, I would point out that as long as the policy for blinded reviews remains optional, there clearly is an advantage for more established and well-known investigators or laboratories to remain identified, while there is an incentive for less well-known and established investigators to remain unidentified. Accordingly, reviewers receiving unidentified manuscripts may have a tendency to presume they come from less well-known centers and thus may grade them more harshly than they would manuscripts from well-known investigators or centers. It seems, therefore, that for the blind review policy to work as intended all reviews must be blinded, and that this cannot be an optional policy on the part of either editors or investigators.

Henry Gewirtz, MD
Providence, Rhode Island

ENHANCEMENT OF LEFT VENTRICULAR FUNCTION BY GLUCOSE-INSULIN-POTASSIUM IN ACUTE MYOCARDIAL INFARCTION

I read with great interest the report, "Enhancement of left ventricular function by glucose-insulin-potassium in acute myocardial infarction," by Whitlow et al. I consider the report excellent, but an injustice is evidently manifested. No reference is made to the work of Demetrio Sodi-Pallares, a pioneer in the investigation of glucose-insulin-potassium solutions.

Sodi-Pallares demonstrated a marked improvement in reduced myocardial contraction at the center of a recent myocardial infarction with glucose-insulin-potassium solutions. The study was performed in 1964 with the strain gauge method (Brodie bridge) and was described in the book, "Ischaemic Heart Disease and Polarizing Treatment. New Metabolic and Thermodynamic Bases," published by Tampa Tracings in 1976.

David Contreras, MD
Juarez, Mexico

REPLY: We are certainly cognizant of the pioneering work of Demetrio Sodi-Pallares and his colleagues in the investigation of glucose-insulin-potassium infusion. Indeed, at our institution, interest in glucose-insulin-potassium infusion began after a lecture on the subject here by Dr. Sodi-Pallares. His work has been referenced in many of our previous publications on this subject,[1–4] all of which were included in our manuscript. The lack of direct reference to the work of Dr. Sodi-Pallares and his colleagues in our most recent report in this Journal[5] was certainly not a comment on the quality and importance of their work. We certainly share their enthusiasm in the use of glucose-insulin-potassium infusion in the setting of acute myocardial infarction.

Patrick L. Whitlow, MD
William J. Rogers, MD
Birmingham, Alabama

1. **Rogers WJ, Stanley AW, Breinig JB, Prather JW, McDaniel HG, Moraski RE, Mantle JA, Russell RO Jr, Rackley CE.** Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin-potassium infusion. Am Heart J 1976;92:441–454.
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GERONTOLOGIC PHARMACOLOGY

We would like to bring to the attention of the scientific research community a recent report[1] of a workshop on gerontologic pharmacology and of a National Institute on Aging Pharmacology Program announcement[2] based on its recommendations. It has been widely reported that the elderly have a greater incidence of adverse side effects of drugs and of drug interactions than do young adults. Evidence has been reported of altered patterns of drug distribution and responsiveness in the elderly. Because drugs are generally tested in young adults and dosage adjusted to their needs, it is not surprising that the elderly may respond differently. Much research is needed to determine where age-related alterations in drug responses exist and, when found, to determine their cause or causes. Studies are encouraged in both clinical and basic research areas. The addition of cohorts of elderly to ongoing studies may be an appropriate means of detecting significant differences, and special National Institute on Aging programs are available for the performance of pilot studies.

George M. Steinberg, PhD
Bethesda, Maryland

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* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

STATE OF MARYLAND PACEMAKER EXPERIENCE (1979–1980): CONFLICTING VIEWS REGARDING THE FREQUENCY OF UNNECESSARY PACEMAKER IMPLANTS

In their article in the January 1, 1983 issue,[1] Scherlis and Dembo report the results of a study that attempts to refute our report on unnecessary pacemaker implants in Maryland. Before raising specific objections to this article we would like to briefly summarize the purpose, findings, and conclusions of our study.

Using the diagnoses the attending physician listed on the face sheets of the charts of all Maryland patients who were given permanent pacemakers in 1979 and 1980, we attempted to determine whether or not there was adequate justification for pacemaker implantation. We identified 7 diagnoses that we considered adequate justification for pacemaker implantation and 9 others that were possible justifications only under appropriate circumstances. A patient with at least 1 of the 7 justifiable diagnoses listed on the face sheet of the medical record was considered an "appropriate" candidate and a patient with at least 1 of the other 9 diagnoses was considered a "questionable" candidate for a pacemaker. A patient that lacked at least 1 of the 16 diagnoses was considered to have been given a pacemaker unnecessarily.

In choosing this methodology we were aware of its limitations. We knew that determining the need for a pacemaker is an inexact science and that need cannot always be determined strictly by reference to diagnoses. We also knew that additional information contained within the medical records would result in crossovers from 1 category to another (for example from "unnecessary" to "appropriate" or vice versa), and we clearly pointed this out in the report. For this reason we were very liberal in our allowable criteria. For example, any patient with a diagnosis of syncope was considered an appropriate candidate for permanent pacing even though this diagnosis may not have been causally related to a cardiac arrhythmia. In essence, we gave the physician the benefit of the doubt at almost every turn.

As reported by Scherlis and Dembo, our study found that in 1979 and 1980, 23% of the pacemakers implanted in Maryland patients were not justified by the diagnoses contained on the face sheet of the medical record. An additional 13% were found to be "questionable" and the remaining 64% were considered "appropriate."

Based on these findings we made 2 recommendations. First, we recommended that the Health Care Financing Administration, which through Medicare pays for approximately 80% of the permanent pacemakers implanted in Maryland, require a second opinion as a condition of reimbursement. We also suggested that Professional Standards Review Organizations (PSROs) establish criteria for pacemaker insertion and review the implants performed at the hospitals under their jurisdiction to ensure that these devices are implanted for appropriate reasons. Neither of these 2 recommendations is extreme; indeed, they would not only reduce the incidence of unnecessary implantations but also educate physicians on appropriate indications for pacing.

In response to our study, Scherlis and Dembo criticized our method and, at the same time, attempted to determine the actual incidence of unnecessary pacemaker implantation in Maryland via chart review. They ultimately determined that unnecessary implantations accounted for 1.4% of all implantations. We think they failed to prove anything of the kind.

While attacking our method as flawed, Scherlis and Dembo fail to acknowledge the obvious bias inherent in the method they employed. As reported by them, each hospital was asked to examine the medical records of patients we labeled unnecessary or questionable recipients of pacemakers to determine whether any diagnosis we identified as justifying implantation, but which was not on the front sheet, was contained in the chart. The clear tone of the letters soliciting the hospitals' cooperation was that this review was to be used to rebut the findings of our study. In fact, the letters to the hospitals from Dr. Scherlis stated explicitly that "(t) here is serious concern as to whether or not the front sheet adequately reflects the complete medical information and justification for pacemaker implantation." It should be apparent that in this context individual hospitals cannot be relied upon to objectively review the medical records of their own pacemaker recipients. The hospitals' bias is overwhelming, and the study fails to take any steps to control for this. The study establishes no guidelines for reviewer selection, the reviewers are not blinded to the purpose of the study, and there are no controlled reviews of even a few randomly selected charts.

Furthermore, as mentioned earlier, our study clearly stated that an examination of the medical records of those patients flagged as "unnecessary" or "questionable" would show that some of them actually needed pacemakers. However, the converse is also true; a number of patients we deemed appropriate candidates for pacing, some based solely on a diagnosis of syncope, probably did not need permanent pacemakers. Scherlis and Dembo did not examine this group. Apparently, they simply assumed that these implantations would have been found appropriate by the chart review method they employed. Thus, they used a double standard, using their own review to change the results with which they disagree, and using our review to sustain the results with which they agree. This is a medically and statistically unacceptable method. As a result, their conclusion that only 1.4% of the permanent pacemakers implanted "might be considered unnecessary or questionable" is simply not valid.

Even more important, however, is the failure of the "chart review" used in the Scherlis and Dembo study to establish standard definitions for such diagnoses as "complete heart block" and "sick sinus syndrome." This is crucial if the need for a pacemaker is to be definitively determined by means of a chart review. For example, while transient atrioventricular block during the postoperative period would be recorded in the medical record as complete heart block, this condition rarely requires permanent pacemaker implantation.[2] Thus, simply finding the diagnosis "complete heart block" somewhere in the chart, even though it may quite properly have been omitted from the face sheet, is no guarantee that pacemaker implantation was justified. For this reason, our study stated that patients deemed "appropriate" candidates for pacers may have actually been given them without adequate justification.

Similarly, while sick sinus syndrome may be an appropriate justification for a pacemaker, it is also a vague and overused diagnosis. In our study this diagnosis was considered an appropriate diagnosis for pacemaker insertion only because of the limitations of the data base. A study purporting to be a chart review, however, must be more critical. As has been pointed out by Marriott and Cozensky,[3] cardiologists, not to mention less trained physicians, have a marked tendency to overdiagnose atrioventricular block and sick sinus syndrome based on electrocardiograms. Marriott and Cozensky believe, and we concur, that this failing is an important cause of unnecessary pacemaker implantation.[4] Furthermore, the diagnoses "found" in the chart may have been tentative and subsequently discarded by the physician and therefore would not appear on the face sheet. Since the reviews in the Scherlis and Dembo study generally do not appear to have been conducted by cardiologists, much less by experts in cardiac pacing, these factors could not have been considered and the authors cannot properly claim, as they did, to have determined the actual incidence of unnecessary pacemaker implantation.

Scherlis and Dembo also state that 20% of the diagnoses listed on the face sheet were so vague that they were "subject to misinterpretation by the coder." The authors do not state whether these diagnoses actually were misinterpreted. Nor do they determine how often the coder misinterpreted diagnoses in cases we labelled "appropriate."

We have never represented our study as the definitive statement on unnecessary pacemaker implantations. In fact, we have been careful to point out the limitations in our data. While some of Scherlis and Dembo's points are valid, and were acknowledged in our report, we were astonished to learn that in 53% of the charts surveyed, the physician simply failed to include on the summary face sheet a diagnosis that would justify the need for a device and procedure costing more than $7,000.

In a conversation with Scherlis before the completion of his study, we expressed our willingness to facilitate a study that would allow expert and distinterested cardiologists to review the charts of Maryland patients receiving permanent pacemakers. Such a review would include patients from the groups identified as "unnecessary" and "questionable" as well as from the group found "appropriate." Scherlis declined this offer, preferring instead to conduct an independent study for the express purpose of refuting our work. Looked at in this light, his results are not surprising. Consequently, the incidence of unnecessary pacemaker implantation as determined by a proper chart review remains to be determined. To that

end, our offer to cooperate in a thorough study of the issue still stands.

Peter R. Kowey, MD
Allen Greenberg, JD
Eve Bargmann, MD
Sidney M. Wolfe, MD
Washington, D.C.

1. **Scherlis L, Dembo DH.** Problems in health data analysis: the Maryland permanent pacemaker experience in 1979 and 1980. Am J Cardiol 1983;51:131–136.
2. **Chardack W.** Cardiac pacemakers. In: Sabiston D, ed. Davis-Christopher Textbook of Surgery. Philadelphia: WB Saunders, 1972:2090.
3. **Marriott HJL, Cozensky G.** Arrhythmias in coronary care: a renewed plea. Heart and Lung 1982;11:33–39.
4. **Marriott HJL.** Personal communication, August 18, 1982.

REPLY: The original report by the Health Research Group contained allegations about the unnecessary implantation of permanent pacemakers in Maryland. In describing their methodology which was based on "face sheet" information only, they now state that they "... were aware of its limitations." In their original report, they state that "even with the limitations inherent in our study—limitations which probably resulted in an underestimate of the problem—we believe that we have uncovered a serious problem that wastes millions of Government and private health care dollars every year." Further, they do state that an examination of the medical record "... would likely result in some crossovers from one category to another. But because of our liberal criteria, we believe that more patients would go from "appropriate" or "questionable" to "unnecessary" than from "unnecessary" to either of the other 2 categories." Such preconceptions without subsequent documentation are difficult to accept. The release of their study did not adequately include the limitations which they now emphasize. The Health Research Group's recommendations were based on unconfirmed allegations and should be evaluated on that basis.

We are accused of failing to acknowledge the "... obvious bias inherent in the method" we employed. We had prior experience with such activities as peer review, mortality studies, focused review, utilization review, professional service review organization activities, and quality assurance programs—all of which utilize face sheet data. We have been aware of the shortcomings of this source of information as a determinant of quality of care or appropriateness of procedures. The letter sent to the cooperating hospitals reflected this concern, but the allegations about hospital bias and the resultant inability of individual hospitals to objectively review the medical records because of this letter are unacceptable. Each of the 32 hospitals responded with essential similar data; that is, complete chart review provided the justification for permanent pacemakers which had not been included on the face sheet. As stated in our report, the study was performed as follows. In each hospital, a computer printout of the chart numbers of the medical records to be reviewed was sent to the Quality Assurance Chairman and reviews of the medical record were undertaken by members of the Quality Assurance Committees or, in several instances, members of the Utilization Review Committees, teams of cardiologists, or heads of the Departments of Medicine in their respective hospitals. For each medical record reviewed, the sources of the additional data were provided, that is, consultation notes, operative notes, progress notes, and electrocardiograms. In each hospital, whatever the review mechanism, the reported problems with face sheet data were similar.

With the enormous publicity given the Health Research Group study in the Senate, in the lay press, and on television, blinding of the reviewer about the purpose of the study was impossible. Our study had very straightforward goals: "... to determine the validity of using only face sheet data for the determination of appropriateness of procedures. Additional consideration was given to the general problem of trying to establish guidelines for pacemaker insertion." We used *exactly* the same criteria employed by the Health Research Group for pacemaker insertion and clearly stated this.

In several instances, the indications listed by the Health Research Group are not as rigid as we would have liked were we to have initiated a similar study. We therefore utilized exactly the same criteria as they did but used the entire chart as a source of information and not only the face sheet. Hence, we did not define sick sinus syndrome, complete atrioventricular block, or syncope. We did not review all of the charts of the patients who received permanent pacemakers in Maryland in 1979 and 1980 but only those which fulfilled the Health Research Group criteria of "questionable" or "unnecessary." It may be true that there were errors in charting in that group as well, but a detailed chart review of those characterized as "questionable" or "unnecessary" was given the first priority in view of the allegations by the Health Research Group as related to these 2 categories. We had no "double standard" and clearly stated our methodology. In response to the query about those diagnoses which were so vague that they were "subject to misinterpretation by the coder," these diagnoses actually were misinterpreted and were so classified. Again, we did not review the charts of those patients who were characterized as "appropriate" and therefore cannot state how often the coder misinterpreted diagnoses in these cases. We would not be surprised were there to be errors in those patients as well.

We did ask the reviewers of the medical charts to state whether, after final analysis of the total medical record, they felt that the pacemaker insertions were or were not justified. As we stated in our study, "In a few instances, the hospital reviewers commented that the pacemaker insertion was judged appropriate although the criteria enumerated in the Health Research Report were not present. The authors, however, included all of these cases as being inappropriate for the purpose of this report and in order to make a direct comparison of face sheet data with complete medical record review." There are accepted criteria for pacemaker insertions in addition to those listed in the Health Research Group report and which we discussed in our study. Our primary purpose was to determine the validity of the utilization of face sheet data to determine the appropriateness of permanent pacemaker insertion. We concluded that such face sheet data cannot be used for this purpose.

The authors of the Health Research Group have indeed performed a valuable function for the medical community and for health related groups. Their study served as the basis for our report which demonstrated that face sheet data are unreliable. They are "astonished" that diagnoses which justified procedures costing $7,000 are omitted from the face sheet. We are not since the face sheets have not served as the vehicle for physician reimbursement. This astonishment is only the initial phase of an educational process for them and for many health care providers who are beginning to understand the poor quality of face sheet data. Although their study is flawed by the use of such data, we are indebted to them for providing the impetus to again demonstrate the problems inherent in the analysis of such data.

As to the private conversation referred to, it occurred while our study was already in progress. The cooperation of the Health Research Group was not needed to facilitate our study, which was designed to be a study independent of the original report. Maryland has expert cardiologists, many of whom were involved in this study in their respective hospitals. These hospitals included both medical schools in Maryland as well as 30 additional community hospitals of varying sizes.

The track record of the Health Research Group is not one which encourages cooperation or confidence in its ability to participate in health research where a knowledge of technical terminology, chart problems, or face sheet data is concerned.

Leonard Scherlis, MD
Donald H. Dembo, MD
Baltimore, Maryland

AORTOCORONARY BYPASS IN ASYMPTOMATIC OR MILDLY SYMPTOMATIC CORONARY PATIENTS

Since aortocoronary bypass operations first came into use, attempts have been made to evaluate the prognosis of patients with medically treated coronary heart disease (CAD). Although mortality figures are usually presented for 1-, 2-, and 3-vessel CAD, it became apparent that left ventricular function, expressed in terms of ejection fraction, is a more potent discriminator of poor risk patients than are the number of vessels involved by the atherosclerotic process. The most convincing data, based on >20,000 patients (Coronary Artery Surgery Study),[1] showed an annual mortality of patients with 3-vessel disease of 7% and that of the subset with good left ventricular function, 3.6%.

The study by Kent et al[2] addresses the prognosis of 147 medically treated patients with CAD who were asymptomatic or mildly symptomatic. This study generally confirms the good prognosis of patients in this category. However, the authors found a subset of patients with an "extremely grave" prognosis,

namely, those with 3-vessel CAD and poor exercise capacity for whom they recommend bypass surgery without further randomized study. Most patients in this subset showed good ejection fractions.

This conclusion differs from others. The entire series shows a peculiar distribution of fatal cases: With a 4-year follow-up, 7 of the 8 deaths occurred during the first year. Of these, 5 were in the "extremely grave" subset, which involved only *17 patients* (5 deaths and 12 survivors in 1 year). The authors calculated a 9% annual mortality for this subset. This is incorrect: it is roughly a 30% first-year mortality, a figure so striking that it almost certainly indicates a powerful hidden bias in the series or perhaps a freak chance occurrence. A question can be raised whether a population referred to a cardiac center, regardless of reasons for the referral, can ever be considered a random sample.

Asymptomatic patients especially should not be recommended for bypass surgery on the basis of experience with a few cases, but require solid data and convincing evidence. If "poor exercise capacity" is an important discriminating factor (which I doubt), a major investigation of this problem is in order.

Arthur Selzer, MD
San Francisco, California

1. **Mock MB, Ringqvist I, Fisher L, et al.** The survival of nonoperated patients with ischemic heart disease: the CASS experience (abstr). Am J Cardiol 1982;49:1007.
2. **Kent KM, Rosing DR, Ewels CJ, Lipson L, Bonow R, Epstein SE.** Prognosis of asymptomatic or mildly symptomatic patients with coronary artery disease. Am J Cardiol 1982;49:1823–1831.

REPLY: Selzer raises an important issue which we addressed in a recent report; that is, whether a sufficiently high-risk subgroup of patients with 3-vessel disease can be identified so that a coronary bypass operation can seriously be considered. We did identify such a subgroup: those patients with 3-vessel disease and poor exercise capacity. The overall mortality of patients with 3-vessel disease that we observed was remarkably similar to that of the European Cooperative Study, the medical group of the Veterans Administration Study, and the recently published Coronary Artery Surgery Study. The average annual mortality in our series was 6%, whereas that of the Coronary Artery Surgery Study was 7%. Moreover, we identified a lower risk subgroup with an annual mortality of 4% (patients with good exercise capacity), just as the Coronary Artery Surgery Study did (patients with good left ventricular function, an annual mortality of 4%). If a subgroup with an annual mortality less than the mean is found, it necessarily implies that a subgroup with an annual mortality higher than the mean is present. In our study, this was the subgroup with poor exercise capacity, in which the annual mortality was 9%. Annual mortality of this group was calculated by standard life-table techniques and was expressed for the entire observation period. As Selzer notes, the first-year mortality was high; however, if survival data from most natural history studies are examined, there is frequently a larger mortality in the first year after evaluation, followed by a slow decline. This difference is probably due to selection criteria unknown to the investigators or to the referring physician. Nonetheless, the same selection criteria are probably operative when decisions are made regarding referral of patients with chronic stable angina for invasive studies to any center. Although the number of patients within our subgroup was not large, the poor prognosis of these patients, once identified, was clear. Analysis of radionuclide data from these patients confirms that the patients unable to complete 100 W on the bicycle ergometer were also the patients with a decrement of ejection fraction during exercise. Thus, these patients have a larger amount of myocardium at jeopardy, which may provide a physiologic basis for poor exercise capacity and, perhaps, the likelihood of sudden cardiac death.

Kenneth M. Kent, MD
Douglas R. Rosing, MD
Robert O. Bonow, MD
Carolyn J. Ewels, BS
Stephen E. Epstein, MD
Bethesda, Maryland

FACTORS INFLUENCING LEFT VENTRICULAR HYPERTROPHY IN SYSTEMIC HYPERTENSION

The echographic study by Fouad et al[1] showing that a reversal of left ventricular hypertrophy (LVH) can be achieved during methyldopa treatment even in the absence of either significant or proportional pressure reduction supports the view that factors other than arterial pressure may be involved in both the induction and the reversal of LVH. We[2] found a positive correlation between both resting supine and upright plasma norepinephrine levels (by fluorimetry[3]) and ventricular septal (VS) thickness in borderline hypertensive patients (arterial pressure at rest in systole 140 to 150 mm Hg and in diastole 90 to 95 mm Hg). VS thickness was increased in these borderline patients versus age-matched healthy subjects, whereas posterior wall (PW) thickness was normal. In patients with pressure levels constantly >150/95 mm Hg, VS thickness was significantly increased compared with that of healthy subjects and did not correlate with either norepinephrine or arterial pressure; PW thickness, which was increased in both healthy subjects and borderline patients, correlated with mean arterial pressure but not with plasma norepinephrine levels.

From our data, it is tempting to speculate that septal hypertrophy may be consistently sympathetic-induced, representing an early stage of hypertension-induced LVH which afterwards extends to the left PW where it appears to be mainly afterload-induced. Practical implications include whether diuretics or other agents not reducing sympathetic activity or its effects may be appropriate in borderline patients when one goal of therapy is to limit LVH.

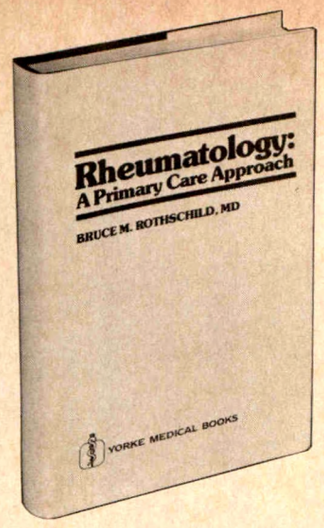
Luigi Corea
Maurizio Bentivoglio
Paolo Verdecchia
Mario Motolese
Perugia, Italy

1. **Fouad FM, Nakashima Y, Tarazi RC, Salcedo EE.** Reversal of left ventricular hypertrophy in hypertensive patients treated with methyldopa. Lack of association with blood pressure control. Am J Cardiol 1982;49:795–801.
2. **Corea L, Bentivoglio M, Verdecchia P, Motolese M.** Left ventricular wall thickness and plasma catecholamines in borderline and stable essential hypertension. Eur Heart J 1982;3:164–170.
3. **Renzini V, Brunori CA, Valori C.** A sensitive and specific fluorimetric method for the determination of noradrenaline and adrenaline in human plasma. Clin Chim Acta 1970;30:587–594.

REPLY: The letter by Corea et al is an interesting and stimulating suggestion regarding the possible role of adrenergic activity in modulating cardiac structural responses to systemic hypertension. This suggestion has been advanced in different modes and with different degrees of evidence since the initial work of Raab.[1–3] Both cardiac hypertrophy and hypertension are multifactorial processes, so that all aspects of hypertensive LVH cannot be explained by 1 factor alone. Rather than conclude from various correlations mentioned that VS and PW thickness respond to entirely different stimuli, it would probably be more physiologic to assume that both arterial pressure and adrenergic factors influence cardiac hypertrophy and its reversal to varying degrees depending on the type of hypertension.[3]

Fetnat M. Fouad, MD
Y. Nakashima, MD
Robert C. Tarazi, MD
E. E. Salcedo, MD
Cleveland, Ohio

1. **Raab W, Lepeschkin E.** Biochemical versus haemodynamic factors in the origin of hypertensive heart disease. Acta Med Scand 1950;138:81–93.
2. **Laks MM, Morady F, Swant HJC.** Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest 1973;64:75–78.
3. **Tarazi RC, Sen S, Saragoca M, Khairallah P.** The multifactorial role of catecholamines in hypertensive cardiac hypertrophy. Eur Heart J 1982;3:Suppl A:103–110.



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Written by:

Bruce M. Rothschild, MD

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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Alfred Soffer, MD
Chief Editor Archives of Internal Medicine

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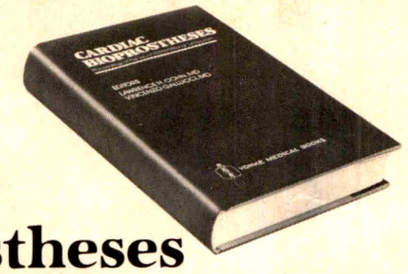

Cardiac Bioprostheses

Proceedings of the Second International Symposium
Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

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Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

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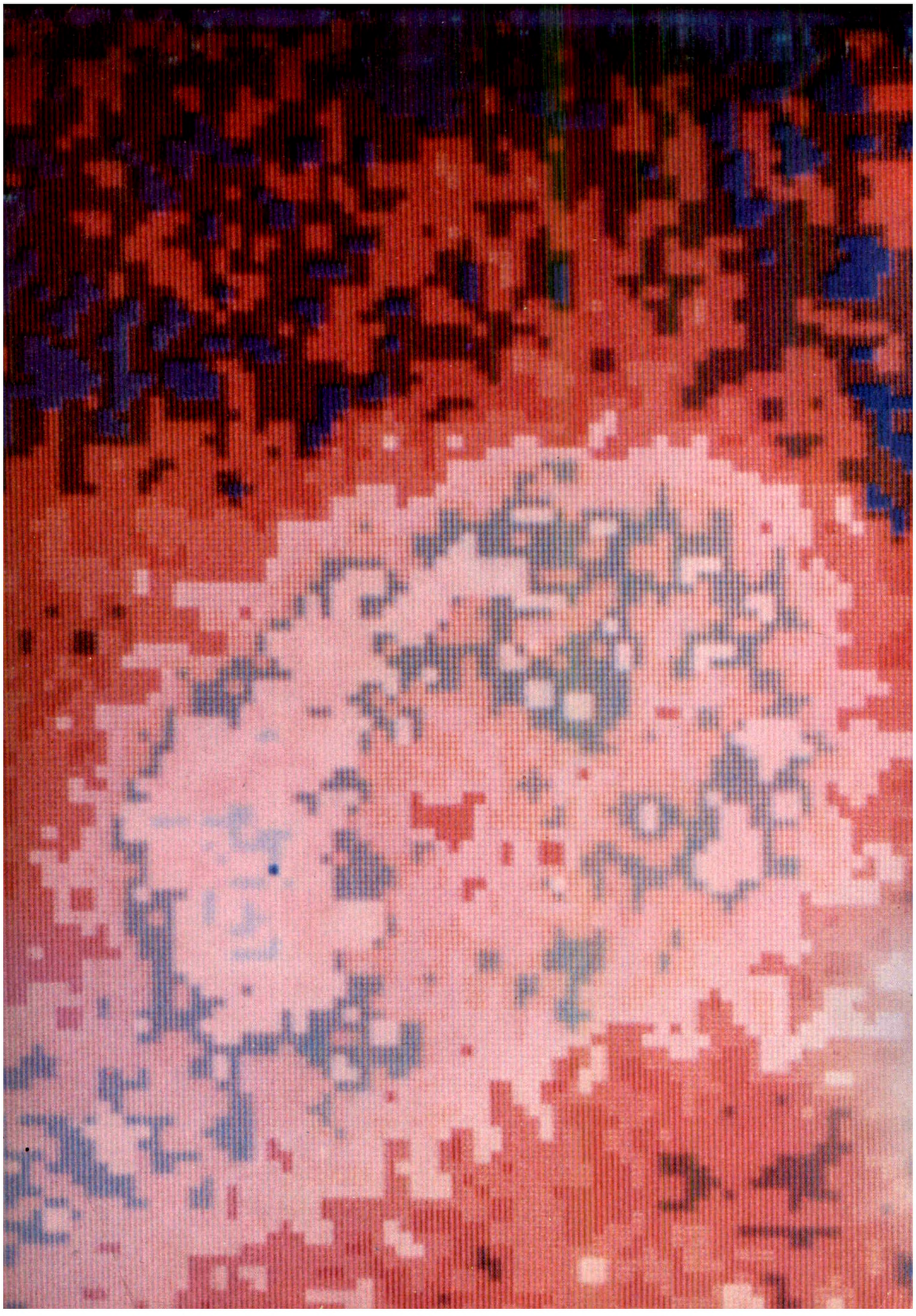

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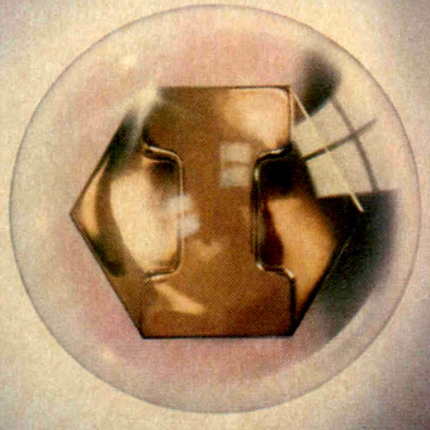

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Propranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

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—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains **10 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).
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The appearance of these tablets is a trademark of Ayerst Laboratories.
Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).
Store at room temperature (approximately 25° C).

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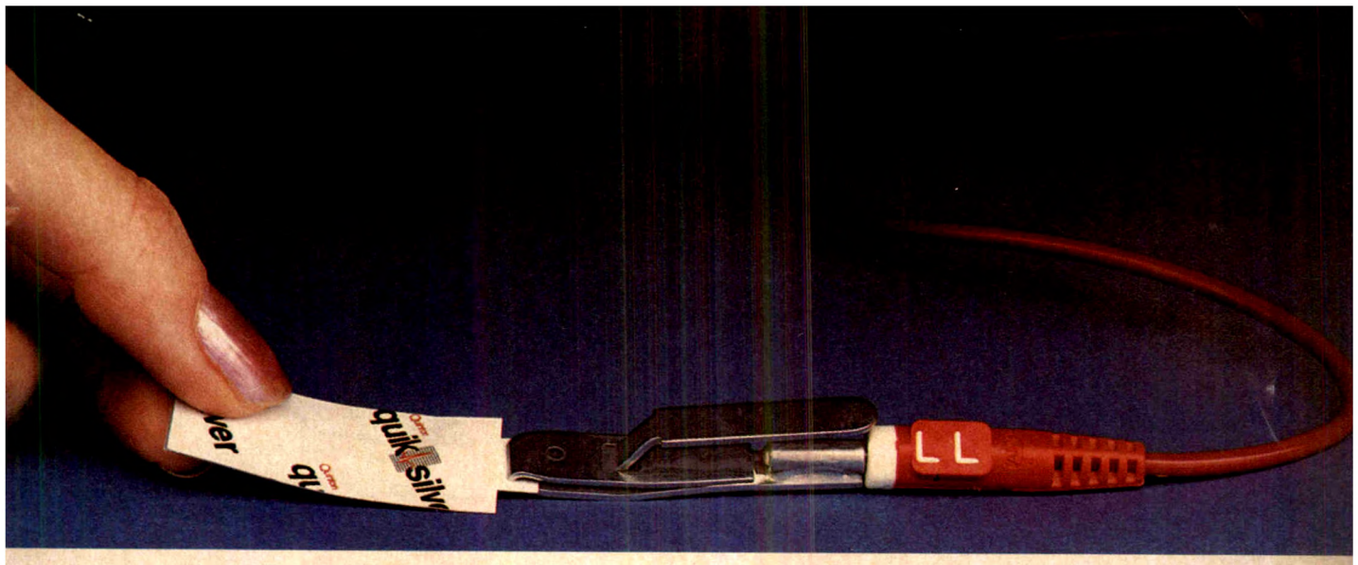

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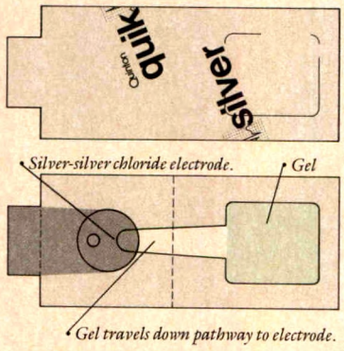

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Serum K+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone; restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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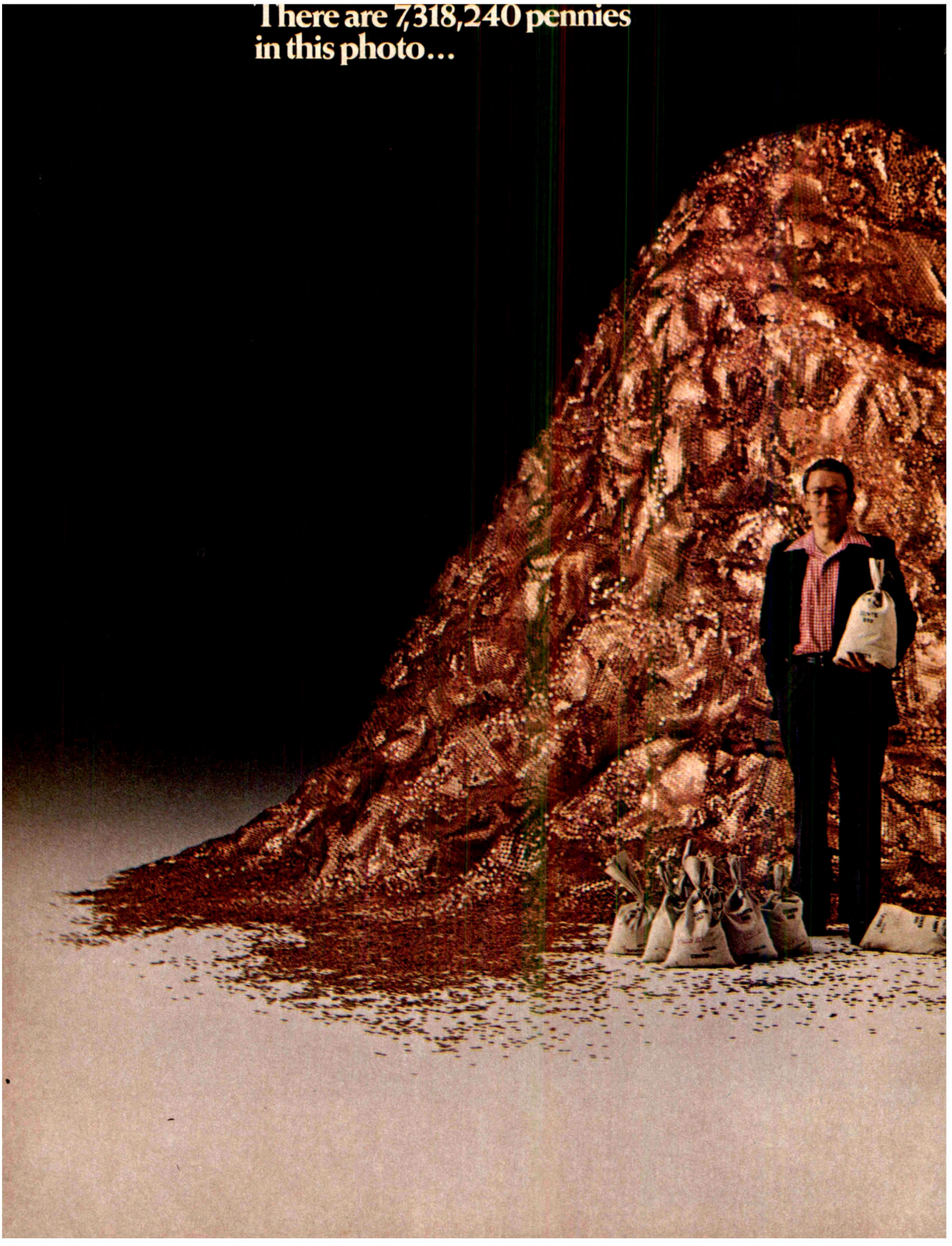
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Slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.
*Based on courses of therapy through 1981. Data on file, CIBA Pharmaceutical Company.
Please see next page for brief Prescribing Information.
CIBA

SLOW-K®
potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

Consult complete product literature before prescribing.

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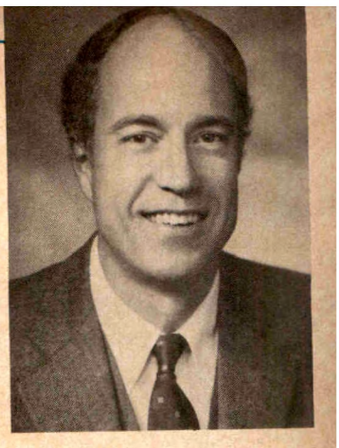

Abbreviations in the AJC

Some editors of medical journals allow abbreviations and others do not. I favor *limited numbers* of *appropriate abbreviations for commonly used terms* in articles submitted to the AJC for 2 reasons: (1) abbreviations save space and, therefore, permit more articles to be published, and (2) abbreviations, if limited to commonly used terms, decrease rather than increase reading time. In general, I prefer to limit abbreviations to 3 per manuscript and to the terms appearing in the manuscript's title.

An upcoming paper in the AJC was entitled "*Left ventricular* response to isometric exercise and its value in predicting the change in ventricular function after *mitral valve replacement* for *mitral regurgitation.*" The phrase "left ventricular" (occupying 16 spaces) appeared 38 times, "mitral regurgitation" (20 spaces) 28 times, and "mitral valve replacement" (24 spaces) 12 times. Spelling out these 3 phrases would have occupied 1,456 spaces, but by abbreviating each (LV, MVR, MR), only 168 spaces were used and 24 single-column lines were saved—an average of nearly 8 column lines per printed page. (Each column in the AJC contains 62 lines and each line, 54 spaces.) Another paper entitled "Relation between the site of origin of *ventricular tachycardia* and relative *left ventricular* myocardial perfusion and wall motion" used the phrase "ventricular tachycardia" (23 spaces) 57 times and the phrase "left ventricular" 42 times. Spelling out these 2 phrases would have occupied 1,983 spaces, but the abbreviations occupied only 198 spaces and 33 single-column lines were saved, an average of >8 column lines per printed page. Another recent paper entitled "Effect of *atrial fibrillation* on atrial blood flow in conscious dogs" used the phrase "atrial fibrillation" (19 spaces) at least 78 times and the single abbreviation "AF" saved 1,326 spaces or >24 lines. Because >40 articles appear now in each regular monthly AJC, averaging 228 text pages per issue, the savings in text pages each month by use of a few abbreviations is enormous, and this saving allows more articles to be published!

Abbreviations must be limited to *commonly recognized terms* (see later). Recently, I reviewed a manuscript which used the abbreviation "LVT," indicating "left ventricular thrombus." "LVT" is not a commonly recognized abbreviation and therefore I changed it to "LV thrombus," abbreviating "left ventricular" throughout but not "thrombus." Incidentally, the most commonly used phrase in cardiologic journals is "left ventricular"; hence, the abbreviation "LV" is highly useful. It should be noted that "LV" most commonly signifies "left ventricular," not "left ventricle," which is far less commonly used.

Not only must abbreviations be limited and of commonly used terms, but they must be *appropriate* in that *each letter of the abbreviation must stand for a single word.* It is inappropriate to use a letter for 1 word in a phrase, then use >1 letter for a second word in the same phrase. Specifically, it is inappropriate to abbreviate "hypertrophic cardiomyopathy" as "HCM"—this abbreviation breaks the rule of parallelism—1 letter stands for 1 word and a separate letter stands for each of 2 major syllables in the second word. The proper abbreviation is "HC." The commonly used abbreviations for the coronary arteries, namely, "RCA," "LAD," and "LCx" are not consistent. If "CA," the abbreviation for "coronary artery," is used after the "right" to read "RCA," then it should be used after the "left anterior descending" to read "LADCA" and after the "left circumflex" to read "LCCA." It is inappropriate to abbreviate 2 syllables in "circumflex" and not follow the same principle for the "anterior descending." It is best to abbreviate "left anterior descending" as "LAD" and "left circumflex" as "LC" (omitting the "x"), but not to abbreviate the "right coronary artery"; simply let it be known as "right."

Occasionally, it is warranted to make exception to the

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abbreviation principle of 1 letter per word. The commonly used abbreviations for "electrocardiogram" (ECG), "atrioventricular" (AV), and "radionuclide angiography or angiocardiography" (RNA) are really inappropriate, but each is so ingrained that they have become appropriate. To abbreviate "electrocardiogram" as "E" or "atrioventricular" as "A" or "radionuclide angiography" as "RA" is confusing. An abbreviation for "echocardiogram" or "echocardiography" is another exception; probably "echo" is the most appropriate abbreviation for either word.

It is best to use certain terms universally to prevent confusion when abbreviating. The term "mitral regurgitation" is better than the term "mitral insufficiency" for several reasons; one is that it allows the abbreviation "MR," which prevents its confusion with "MI," which best stands for "myocardial infarction" or "infarct." Although obviously it would be consistent with the rule of parallelism to abbreviate "coronary heart disease" as "CHD," this might produce confusion with "congenital heart disease" and, therefore, it is preferable to allow "CAD" to signify both "coronary heart disease" and "coronary artery disease." To use the terms "*inter*atrial septal defect" and "*inter*ventricular septal defect" is undesirable because each implies that *extra*atrial or *extra*ventricular septal defects also exist. The prefix "inter" should be discarded. Of course, only 1 atrial septum and only 1 ventricular septum exist. Therefore, the proper terms are "atrial septal defect" (ASD) and "ventricular septal defect" (VSD), not "IASD" and "IVSD." On echocardiograms, the ventricular septum should be labeled "VS," not "IVS."

Finally, once initiated it is important to use abbreviations consistently throughout each page of a paper. When first appearing in both summary and introduction, the phrase to be abbreviated should be spelled out and thereafter abbreviated elsewhere in the manuscript.

Although abbreviations save enormous space, their use results in more time expended by authors, editors, and copy editors to ensure uniformity and appropriateness. It would save all 3 much time and effort if abbreviations were not allowed; but in our era of enormous expense for each published page and limited time to read each page, it is only proper that limited numbers of appropriately used abbreviations be permitted in manuscripts.

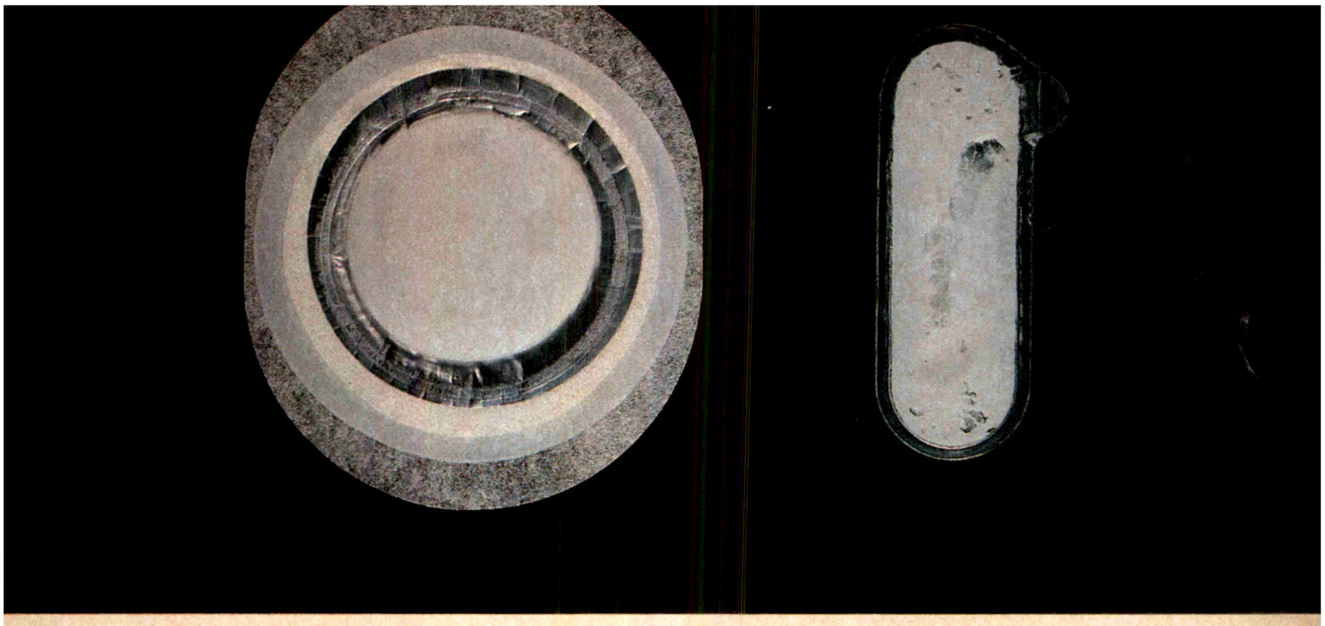
Some of the most commonly used standard cardiologic abbreviations are listed at right.

TERMS COMMONLY ABBREVIATED

AF	= atrial fibrillation
AR	= aortic regurgitation
AS	= aortic stenosis
ASD	= atrial septal defect
AV	= atrioventricular
AVR	= aortic valve replacement
BBB	= bundle branch block
BP	= blood pressure
CABG	= coronary artery bypass grafting
CAD	= coronary heart disease
CHF	= congestive heart failure
Coronary arteries:	
LAD	= left anterior descending
LC	= left circumflex
LM	= left main
ECG	= electrocardiogram
echo	= echocardiogram or echocardiography
EF	= ejection fraction
HC	= hypertrophic cardiomyopathy
LV	= left ventricular
MI	= myocardial infarct or infarction
MR	= mitral regurgitation
MS	= mitral stenosis
MVP	= mitral valve prolapse
MVR	= mitral valve replacement
PA	= pulmonary artery
PDA	= patent ductus arteriosus
RNA	= radionuclide angiocardiography
RV	= right ventricular
TF	= tetralogy of Fallot
TGA	= complete transposition of the great arteries
TR	= tricuspid regurgitation
VF	= ventricular fibrillation
VPC	= ventricular premature complexes
VSD	= ventricular septal defect
VT	= ventricular tachycardia
WPW	= Wolff-Parkinson-White syndrome

William C. Roberts

William C. Roberts, MD
Editor-in-Chief



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CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

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PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

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PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

References

1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc. 01/83

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Dialog of the Hearts –by Hemingway:

"And she smiled and from no distance said, 'Hello, my Inglés.'

'I'm not an Inglés', he said very lazily.

'Oh yes, you are', she said. 'You're my Inglés', and reached and took hold of both his ears and kissed him on the forehead.

'There', she said. 'How is that? Do I kiss thee better?'

Then they were walking along the stream together and he said, 'Maria, I love thee and thou art so lovely and so wonderful and so beautiful and it does such things to me to be with thee that I feel as though I wanted to die when I am loving thee'.

'Oh', she said. 'I die each time. Do you not die?'

'No. Almost. But did thee feel the earth move?'

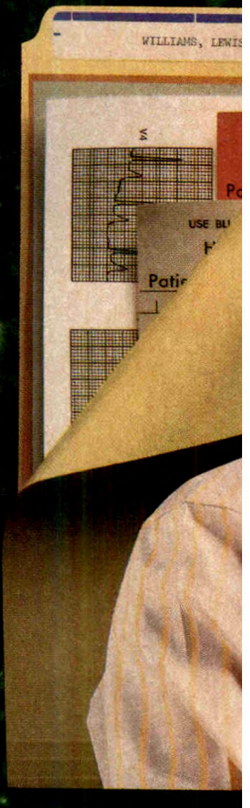
'Yes. As I died. Put thy arm around me, please'.

'No. I have thy hand. Thy hand is enough".

The Dialogue of Robert Jordan and Maria from "For Whom the Bell Tolls".

Another Dialog soon to appear—by Siemens.

LOOKING BENEATH THE SURFACE...



may reveal the cause of his hypertension...

In their study of the humoral mechanisms involved in hypertension, researchers are focusing not only on the kidneys and adrenal glands but on other glandular bodies as well.

Recently, a new aldosterone-stimulating factor (ASF) has been isolated from normal human urine.* Through immunofluorescence, ASF—a glycoprotein with a number of similarities to ACTH and angiotensin II—has been traced to the pituitary gland. By helping to raise plasma levels of aldosterone, which in turn leads to increased renal sodium retention, ASF presumably contributes to hypertension. The importance of its role must still be determined—and eventually will be, as researchers continue to look "beneath the surface."

*Sen S *et al: Hypertension 3*(Suppl 1):81-86, May-Jun 1981. By permission of the American Heart Association, Inc.

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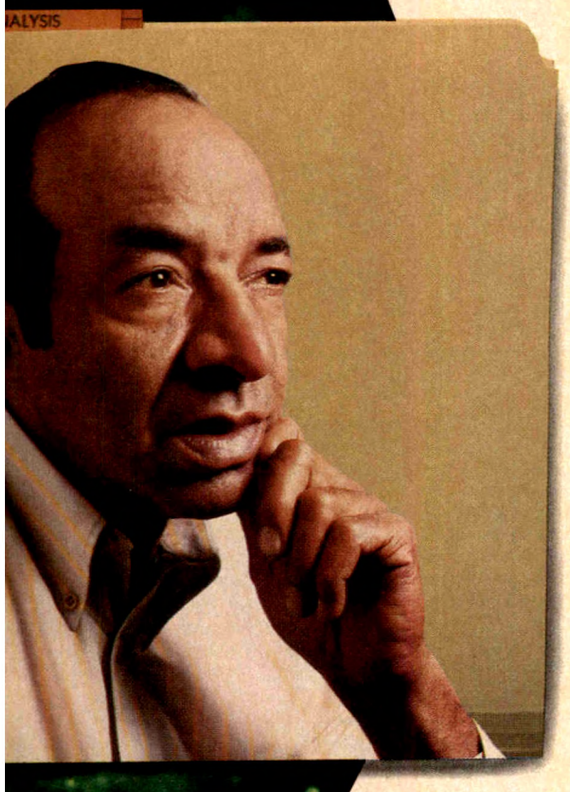

as well as the cause of his excessive anxiety

When the hypertensive patient also has anxiety which may cause him to resist, or even ignore, his medical regimen, discreet probing often provides sufficient information about possible underlying causes to help you deal with the situation. At times, however, neither counseling nor reassurance seems to work. The patient remains tense, apprehensive and—perhaps most damaging of all—noncompliant.

In such cases, adjunctive Valium (diazepam/Roche) can be distinctly helpful. Valium works promptly and dependably to relieve the excessive anxiety that patients may have because of their concern over their organic illnesses. Typically, initial calming occurs within hours—more sustained, decisive relief of anxiety symptoms in just a few days. With his intense anxiety under control, the hypertensive patient may be better able to cope with his problems and to tolerate the demands of his treatment program.

Another important advantage: Valium has been used with most primary cardiac medications, including cardiac glycosides, diuretics and vasodilators. Side effects more serious than drowsiness, fatigue and ataxia are rare and seldom severe. Patients should, of course, be cautioned against drinking alcoholic beverages or driving while taking Valium. Periodic reassessment of the need for psychotropic medication is also recommended.

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Please see summary of product information on the next page.

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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
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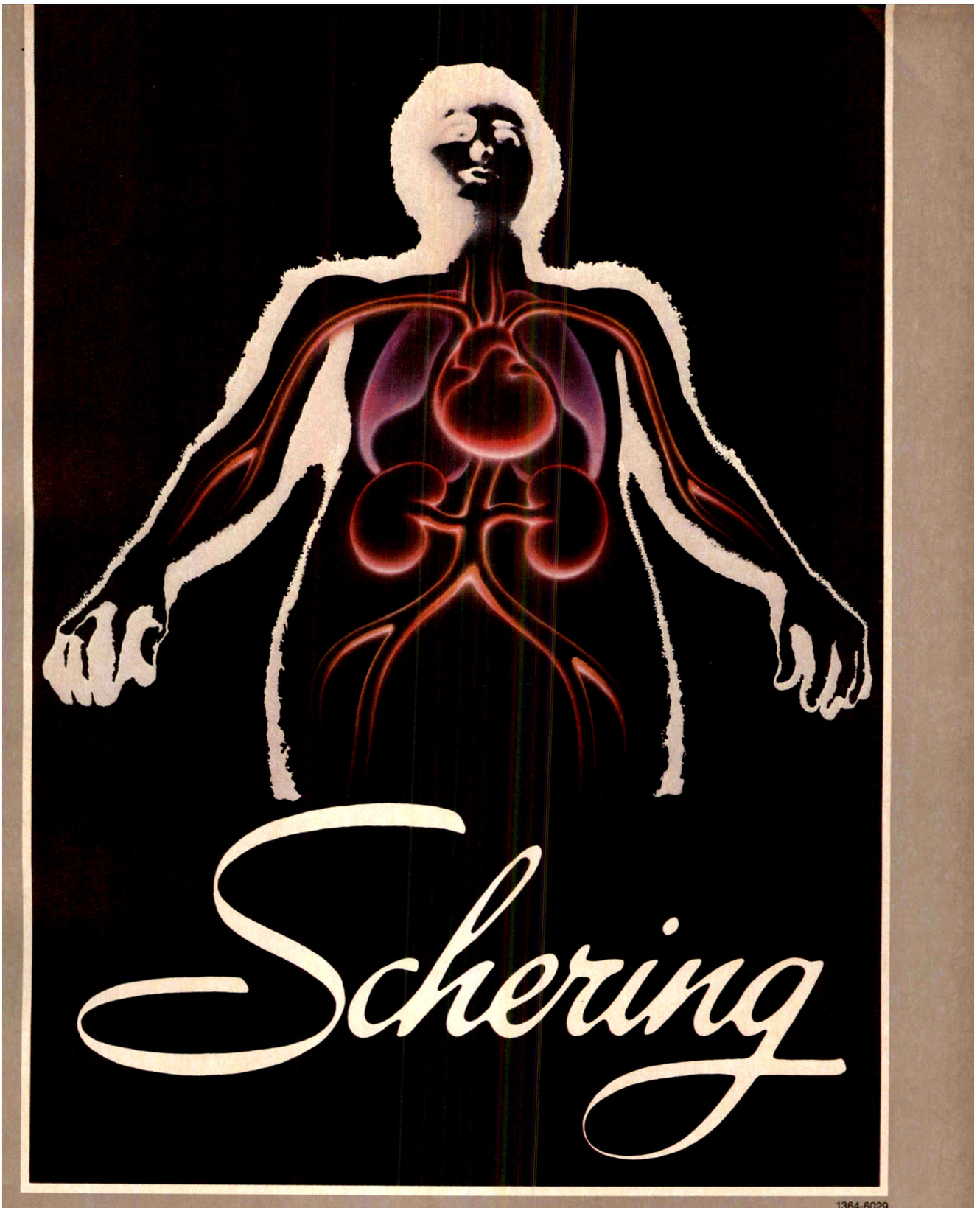

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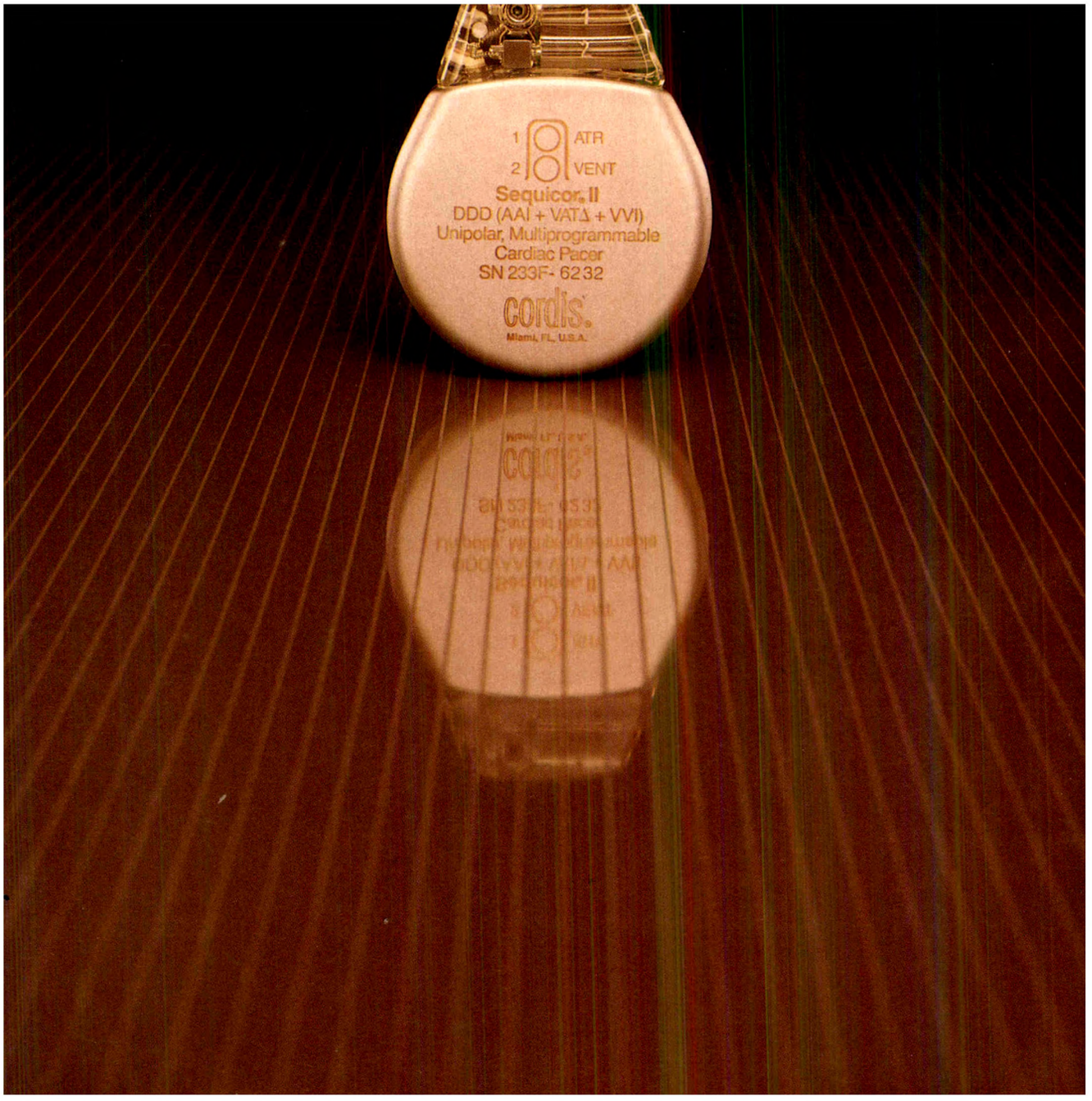
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Pulse duration/ output current, ms/mA (each channel)	0.2/2 0.3/3 0.4/4	0.5/5 0.6/6 0.8/8	1.0/10 2.0/12
A-V delay, ms	75, 100, 125, 150, 175, 200, 250		
Refractory, ms (each channel)	250, 300, 350, 400, 500		
Output voltage, V (open circuit)	8 mA or higher below 8 mA	8.4 4.0	
Pace limit, ppm	160		
Battery test rates, magnet applied, ppm	70 62½ 52½	Battery satisfactory Battery nearing depletion Backup pacing (VOO) activated	
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Parameters revealed through telemetry	Mode, rate, sensitivity, output current, pulse duration, refractory period, and last two digits of pacer serial number.		

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The medical literature describes currently accepted indications and contraindications for various pacing/sensing modes. The physician's clinical experience and judgment must ultimately be the guide in selecting the pacing mode best suited to the patient's needs.

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Atrial-synchronized ventricular pacing (VVD) is indicated for permanent or intermittent complete heart block with normal atrial rhythm. A-V sequential (DVI) pacing is indicated for permanent sinus bradycardia with or without heart block. Automatic dual-chamber demand pacing (DDD) is indicated when there is an A-V conduction disturbance and/or sinus node dysfunction (sinus bradycardia with A-V block or bradytachy syndrome). These atrial pacing modes are intended for patients who would benefit from the restoration of atrial contribution to cardiac output.

Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated for use in the presence of persistent atrial flutter or atrial fibrillation.

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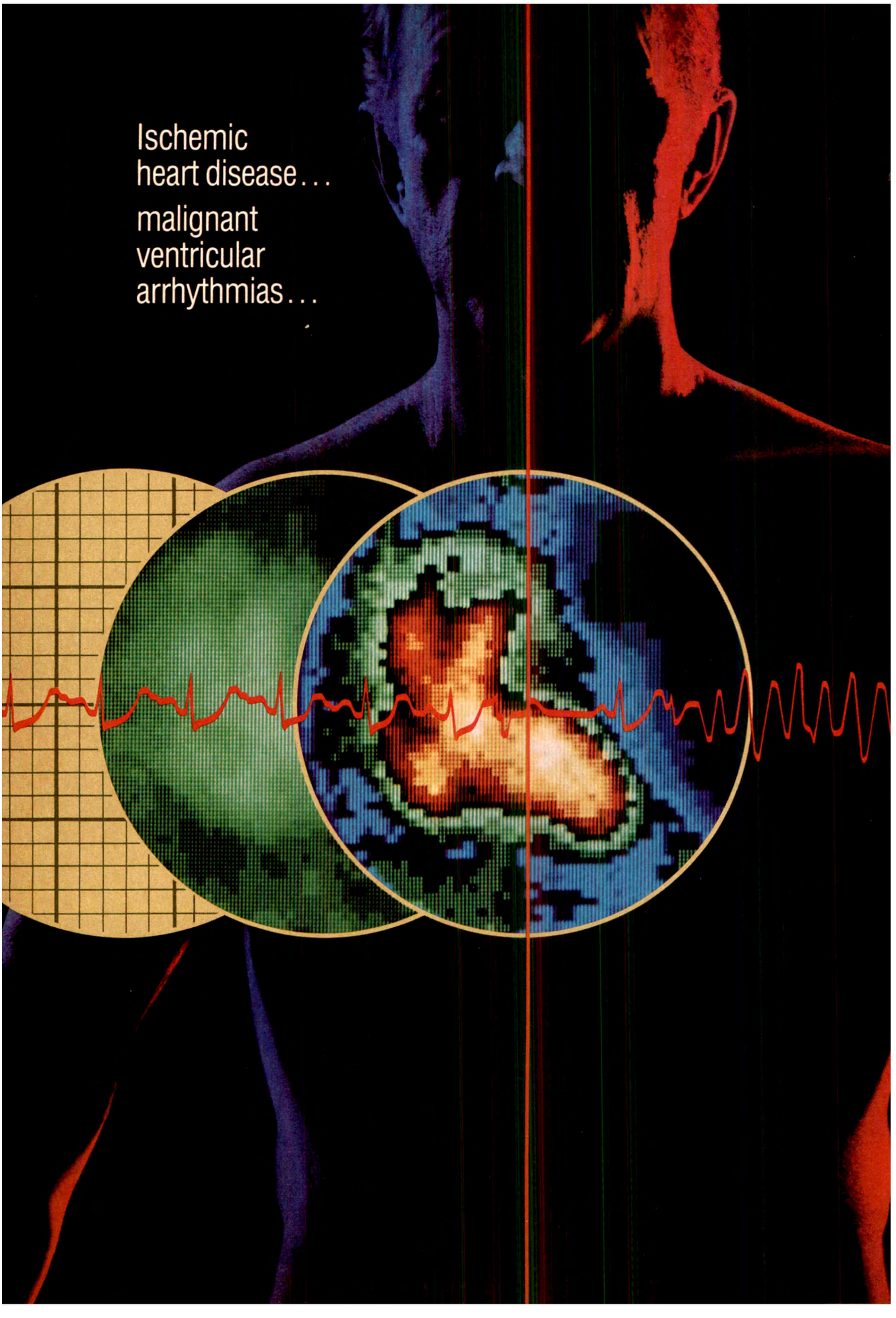
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References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

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QUINAGLUTE® (quinidine gluconate) DURA-TABS®

INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:

1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).

2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.

3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.

7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.

Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.

ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.

Less frequently encountered adverse reactions:

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.

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CONTENTS

CORONARY HEART DISEASE

1045 Late Prognostic Value of Scintigraphic Parameters of Acute Myocardial Infarction Size in Complicated Myocardial Infarction Without Heart Failure

ELIAS H. BOTVINICK, JUAN F. PEREZ-GONZALEZ, RICHARD DUNN, THOMAS PORTS, KANU CHATTERJEE, and WILLIAM PARMLEY

Scintigraphic quantitation of infarction, perfusion abnormality, and left ventricular function in 25 patients with acute myocardial infarction but without heart failure demonstrated advanced electrocardiographic rhythm and conduction abnormalities. Acute scintigraphic findings were related to the late clinical follow-up performed an average of 14.4 months later. Scintigraphic measures of the extent of infarction and related perfusion differentiated patients who died on follow-up (n = 8) from survivors (n = 17). Only measures of perfusion abnormalities differentiated symptomatic survivors (n = 9) from those who remained asymptomatic (n = 8). The study indicates that the late course of patients with serious rhythm and conduction disturbances but without heart failure during infarction is valuable. Early scintigraphic measurements of infarction and perfusion but not function appear to differentiate among widely differing prognostic groups. Patient prognosis seems related to the extent of acute myocardial damage, reversible or irreversible, which can best be made by noninvasive scintigraphic evaluation.

1052 Differentiation Between Right and Circumflex Coronary Artery Disease on Thallium Myocardial Perfusion Scanning

HENRY N. NEWMAN, RICHARD F. DUNN, PHILLIP J. HARRIS, GEORGE J. BAUTOVICH, ANDREW F. McLAUGHLIN, and DAVID T. KELLY

Thallium defects in the inferior and lateral walls of the heart were correlated with right and circumflex coronary artery disease in 405 patients who underwent coronary arteriography. Inferior wall defects were associated with right coronary artery disease, whereas lateral wall defects were associated with left circumflex disease. Disease in both right and circumflex coronary arteries was best identified by a combination of inferior and lateral defects. Disease in only 1 of these 2 vessels was best identified by a combination of inferior without lateral defects for the right coronary artery and lateral without inferior defects for circumflex disease. The pattern of defects on thallium scanning identified significant disease in the right coronary artery, the circumflex coronary artery, and both.

1057 Left Ventricular End-Systolic Pressure-Volume Relation. A Combined Radionuclide and Hemodynamic Study

ABDULMASSIH S. ISKANDRIAN, A-HAMID HAKKI, CHARLES E. BEMIS, SALLY A. KANE, BARBARA BOSTON, and ANGELO AMENTA

This study examines the effect of increasing heart rate by atrial pacing on the left ventricular pressure-volume relation using combined radionuclide and hemodynamic measurements. The results indicate that atrial pacing has a positive inotropic effect in normal subjects and that abnormal changes in end-systolic pressure/end-systolic volume in coronary artery disease are more common than changes in ejection fraction with atrial pacing.

1062 Comparison of Slow-Release Pindolol, Standard Pindolol, and Propranolol in Angina Pectoris

JOHN O. PARKER

Twenty-two patients with stable, exercise-induced angina pectoris who were propranolol responders were assessed over a period of 12 weeks during therapy with standard propranolol, 40 mg 4 times daily, slow-release pindolol, 20 mg once daily, and standard pindolol, 10 mg twice daily. Patients maintained diaries of anginal frequency and nitroglycerin consumption and underwent treadmill exercise testing every 2 weeks before the morning medication. There were no significant differences in nitroglycerin consumption or anginal frequency during the 3 treatment programs. The resting heart rates were higher during therapy with pindolol than with propranolol, but no differences were seen between standard and slow-release pindolol. Treadmill walking time to the endpoint of moderate angina, exercise systolic and diastolic blood pressures, and exercise heart rate were similar

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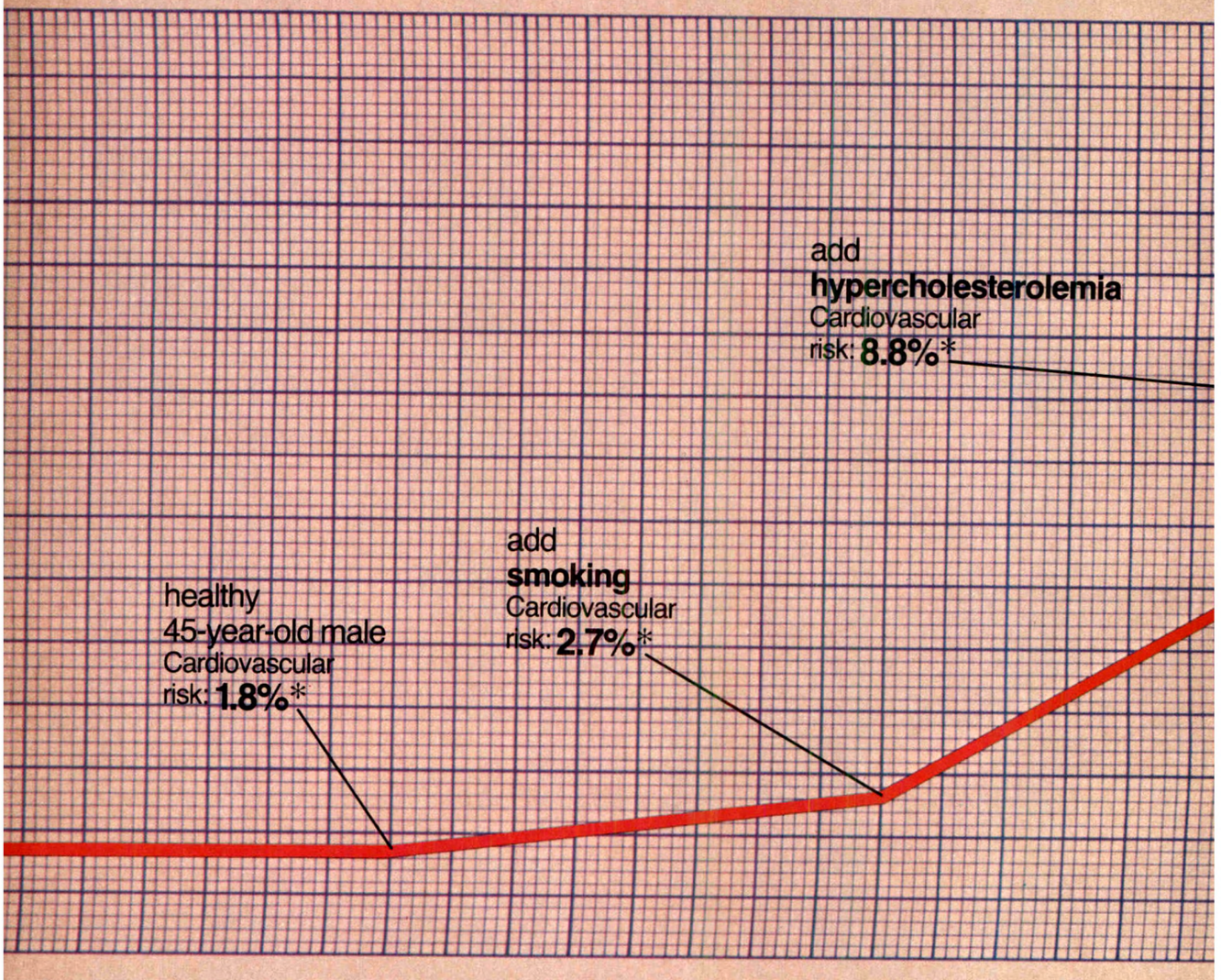
In hypertensive patients



Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

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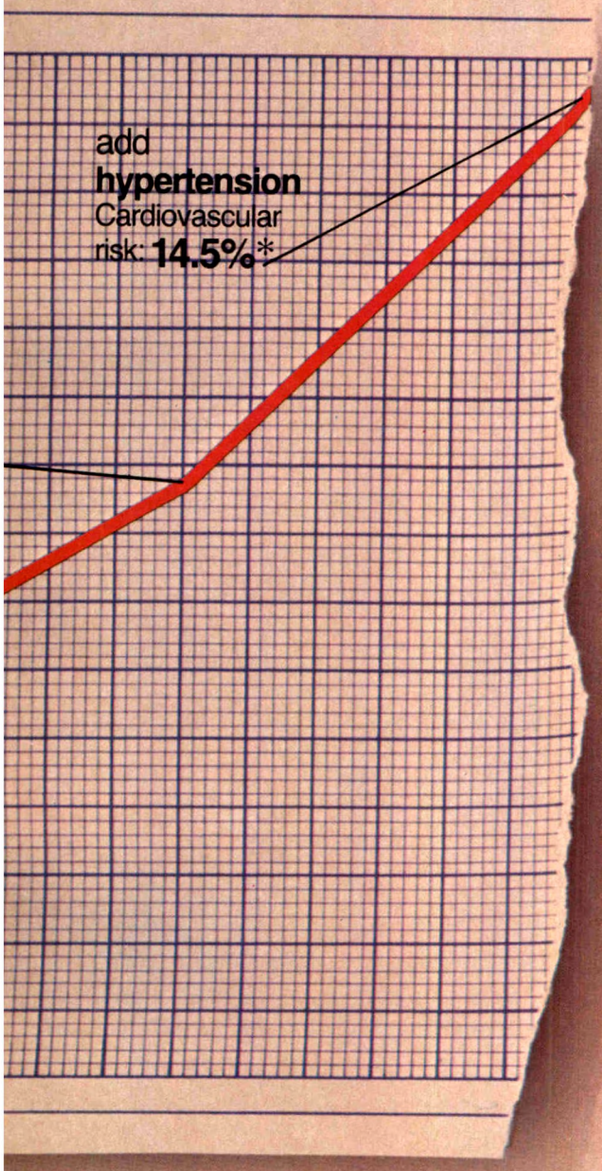

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†Minipress is not indicated for the treatment of hyperlipidemia.

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Minipress® (prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

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WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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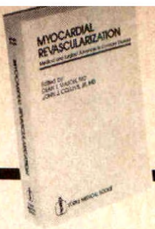

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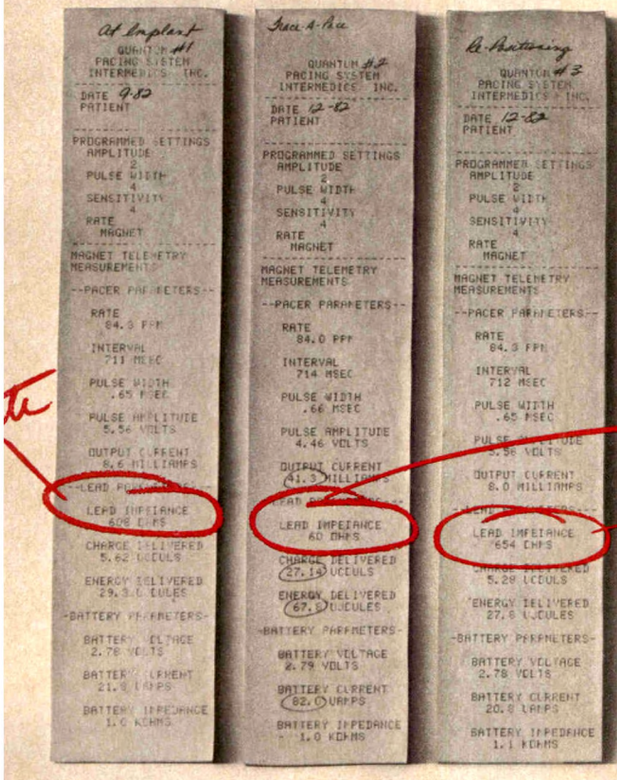
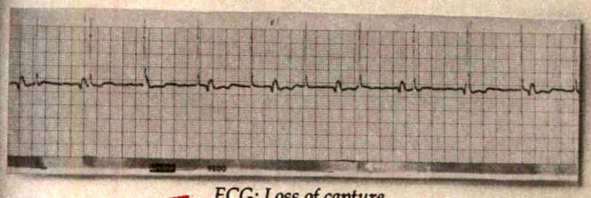
Indication For Pacing: Intermittent Heartblock, Sinus Arrest.

#2 IN A SERIES: QUANTUM—THE PROBLEM SOLVER





ECG: Loss of capture

This is the second in a series of case histories demonstrating the Quantum system's unique ability to help physicians diagnose the condition of a pacemaker patient.

An Actual Case History*

Patient: MALE
Age: 67 YEARS
Indication for Pacing: INTERMITTENT HEARTBLOCK, SINUS ARREST

The patient received a bipolar Quantum™ pulse generator with a transvenous bipolar lead. Intraoperative fluoroscopy and postoperative telemetry indicated satisfactory lead position.

Several months later, during routine telephone follow-up through Intermedics' Trace-A-Pace™ service, the patient's transtelephonic telemetry readout displayed abnormally low lead impedance values. A subsequent ECG strip indicated intermittent pacing, although the patient had experienced no discomfort.

Reexamination revealed insulation fractures of the lead that probably were causing intermittent shorting of the electrode. Access to the lead was gained via the pacer pocket and the repair was effected by medical adhesive and a suture sleeve tied in place. Postrepair pacing is normal with telemetry indicating acceptable lead impedance values.

This is just one example of how Quantum helped pinpoint the exact source of a patient's problem. The complete Quantum pacing system, including a Decoder, Printer, Transmitter, Intermedics Programmer and three pacemaker models, represents the most sophisticated technology available today. By providing you with more information, Quantum helps you better manage your pacemaker patients.

*This actual case history is on record at Intermedics, Inc. For more information, contact the Marketing Dept., Intermedics, Inc.

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during therapy with standard propranolol, standard pindolol, and slow-release pin
these doses, pindolol in either the standard or slow-release formulation is as effec
agement of patients with stable, exercise-induced angina pectoris.

**1067 Frequency and Importance of Unprovoked Coronary Spasm in Patients With
Undergoing Percutaneous Transluminal Coronary Angioplasty**

LAMBERTO G. BENTIVOGLIO, LOUIS R. LEO, NELSON M. WOLF, and STEV

Eleven of 74 candidates for percutaneous transluminal coronary angioplasty (PT
voked spasm superimposed on fixed coronary artery stenosis. Three of the 11, w
nent, were treated medically. The 8 with critical fixed stenosis underwent PTCA, w
no or mild symptoms on follow-up. The rate of success was similar in patients
spasm (6 of 8) and patients without (39 of 63 or 62%). It is concluded that (1) coron
common in single-vessel candidates for PTCA; (2) in patients with critical, fixed co
ated spasm does not reduce the chances of successful PTCA; (3) coronary spasm
of the fixed component of the mixed stenosis and requires long-term vasodilator th
verse effects when PTCA is performed in patients with spasm superimposed on c
nosis appears to justify its use for the time being.

**1072 Assessment of Plexectomy in the Treatment of Severe Coronary Spasm in Pa
Coronary Arteries**

SIMON WEBER, GEORGES-PATRICK DONZEAU-GOUGE, SYLVAIN CHAUVAU
FRANCOIS GUERIN, ALAIN CARPENTIER, and MICHEL DEGEORGES

Surgical denervation of the heart by plexectomy was performed in 3 patients wit
medical therapy with a combination of high-dose nifedipine and nitrates and norma
raphy. In all cases pharmacologic testing, performed postoperatively, established
sion of the autonomic control of the heart; atropine induced no significant tachycard
pressure elicited by phenylephrine induced no reflex bradycardia. In 2 patients, ple
early postoperative period, by severe spasm of the right coronary artery leading to
In the third patient spasm of the right coronary artery recurred 3 weeks postoperat
spite an adequate suppression of the autonomic innervation, plexectomy was in
vasospasm of angiographically normal coronary arteries; the procedure may eve
tients.

**1076 Effects of Early Postmyocardial Infarction Exercise Testing on Self-Perceptio
Physical Activity**

CRAIG K. EWART, C. BARR TAYLOR, LINDA B. REESE, and ROBERT F. DE

Patients' lack of confidence in their ability to resume customary activities after he
disability. Symptom-limited treadmill testing 3 weeks after infarction and a thorou
substantially enhanced confidence (self-efficacy) in 40 consecutive men aged 52 ±
cacy proved superior to peak treadmill heart rate in predicting the intensity and dura
activity in the week after evaluation. Pretreadmill self-efficacy judgments predicte
in turn were altered by treadmill performance: patients whose self-efficacy was
creased after treadmill demonstrated a substantially higher incidence of treadmill a
ues of peak treadmill heart rate and work load than those whose self-efficacy rem
treadmill testing. Treadmill exercise testing provides postinfarction patients with a
tential for physical activity and may diminish medically unwarranted disability in the

**1081 Treadmill Walking Protocol for the Diagnostic Evaluation and Exercise Progra
Patients**

LENORE R. ZOHMAN, JEFFREY L. YOUNG, and ALBERT A. KATTUS

Normative energy cost values for a treadmill test (entirely walking) are presented
tion and MET level to be determined for submaximal and near-maximal steady-state
without direct measurement. Data are applicable to individuals aged 30 to 69 years
ness levels, with or without treadmill experience, who are or are not receiving be
at physicians' offices for performance evaluation or diagnostic exercise testing. Th
trated both as a low-level and maximal exercise performance test with an explanat
formation derived from it into activity guidelines soon after myocardial infarction, o
peutic walking for primary or secondary prevention.

Continued on Page A40

in cardiovascular therapy

New CARDIZEM™ (diltiazem HCl)

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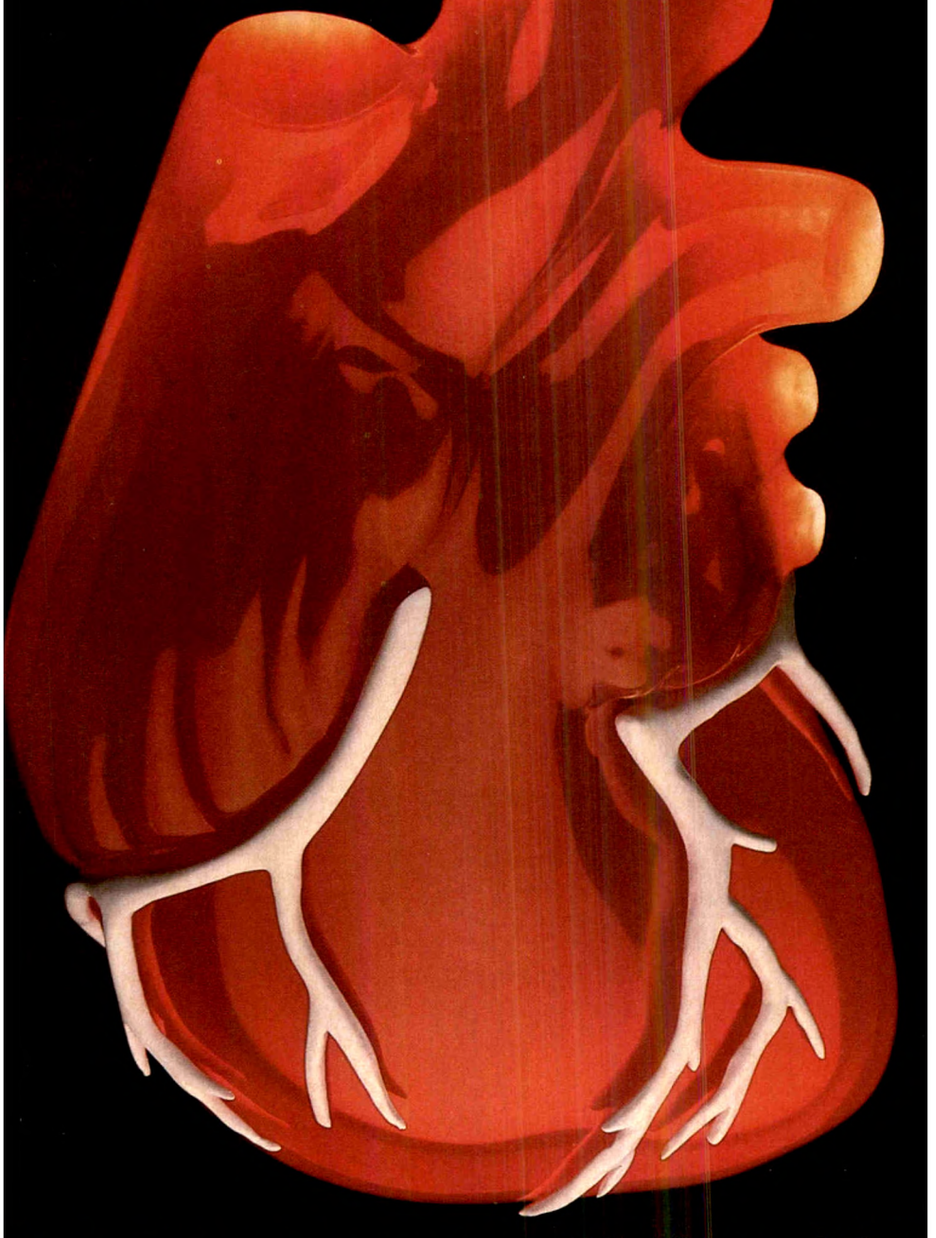

Potent coronary vasodilation with a distinctive hemodynamic profile

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY WITH A LOW INCIDENCE OF SIDE EFFECTS

CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

These changes provide effective therapy with a low incidence of side effects.

Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

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CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries.[1]

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

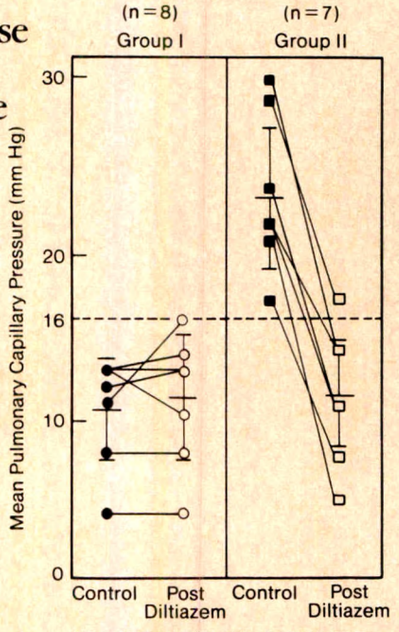
While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.



CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

REFERENCES:

1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.

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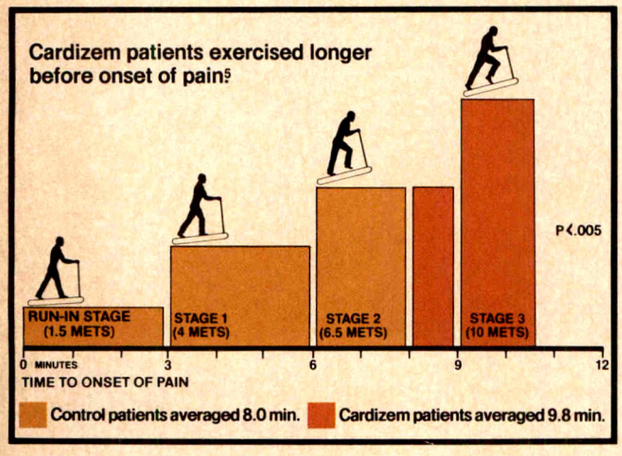
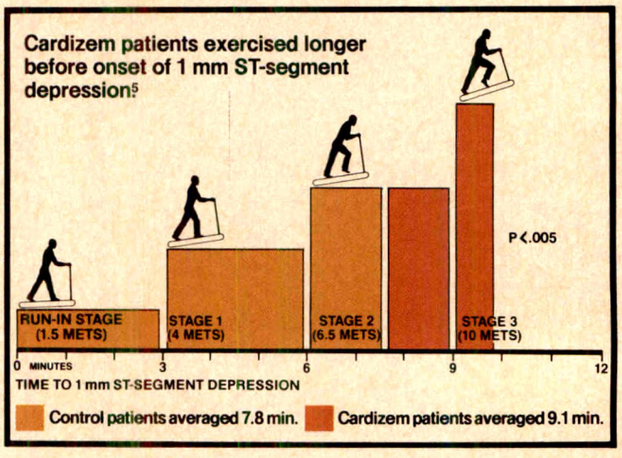
EXCELLENT CLINICAL REPORT TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:
A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

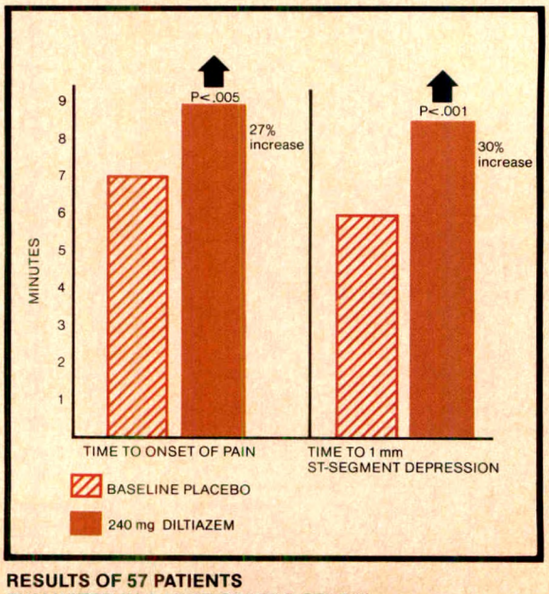
5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.

6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

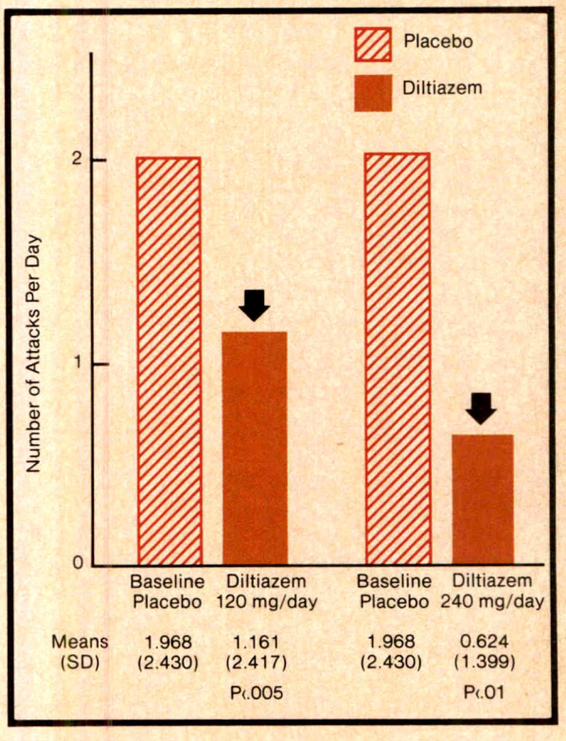
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



7. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

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cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

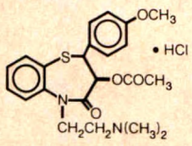
In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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1087 Comparative Functional and Physiologic Status of Active and Dropout Coronary Bypass Patients of a Rehabilitation Program

THAD F. WAITES, EDWARD W. WATT, and GERALD F. FLETCHER

To assess the benefits of regular participation in a medically supervised cardiac rehabilitation program, 22 patients who had undergone coronary artery bypass (2 groups of 11 each) were studied retrospectively. Group I (mean age 53 years) was currently enrolled in the rehabilitation program. Group II (mean age 56 years) had begun but had discontinued the program. The stated reasons for discontinuation were not medical. There was no difference in entry exercise tests, and presurgical catheterization data in both groups were comparable. Mean peak oxygen consumption (VO_2) by modifed Douglas bag technique, heart rate × systolic blood pressure product, and treadmill duration time were recorded in a single testing period. Results revealed that Group I had higher peak VO_2 (30 ml/kg/min) than Group II (24) ($p < 0.005$) and greater treadmill time (11 minutes) than Group II (8) ($p < 0.01$). Nine of 11 subjects in Group I were fully employed, versus 4 of 11 in Group II ($p < 0.01$). One of 11 subjects in Group I had been rehospitalized, versus 5 in Group II. None in Group I but 4 of 11 subjects in Group II smoked. Thus, based on the sampling and methodology of this study, it is concluded that coronary artery bypass patients in rehabilitation programs have greater peak VO_2 and treadmill test time, smoke less, are less often rehospitalized, and are more often fully employed than those who are not in such programs.

1091 Exercise Versus Cold Temperature Stimulation During Radionuclide Cineangiography: Diagnostic Accuracy in Coronary Artery Disease

LAWRENCE J. JORDAN, JEFFREY S. BORER, MICHAEL ZULLO, DAVID HAYES, SPENCER KUBO, JEFFREY W. MOSES, and JOHN CARTER

To assess the relative efficacy of cold temperature stimulation and bicycle exercise in inducing ischemia detectable by radionuclide cineangiography, both stresses were used to study 20 normal subjects and 54 patients with coronary artery disease, 42 of whom had not had myocardial infarction. Regional left ventricular dysfunction was induced by cold in 24 of 41 patients without previous infarction (57%) and by exercise in 34 of 42 patients (81%) ($p < 0.05$), but was absent in all normal subjects during either stress. Using left ventricular ejection fraction as the index of ischemia, sensitivity and specificity of radionuclide cineangiography were assessed over a wide range of ejection fraction changes independently for each stress. During exercise, at ejection fraction changes in which specificity was high, sensitivity also was high, but during cold stress, specificity was relatively poor at ejection fraction changes in which sensitivity was high, and sensitivity was relatively poor when specificity was high.

1098 Ischemia-Associated Intraventricular Conduction Disturbances During Exercise Testing as a Predictor of Proximal Left Anterior Descending Coronary Artery Disease

KEVIN J. BORAN, RENE A. OLIVEROS, CHARLES A. BOUCHER, CHARLES H. BECKMANN, and JOHN F. SEAWORTH

To determine the incidence and significance of transient intraventricular conduction abnormalities occurring in association with myocardial ischemia during exercise testing, the recordings of 2,200 consecutive exercise tests were reviewed. Ten patients (0.45%) were identified as having both ischemia and intraventricular conduction abnormalities that developed transiently during the test. All 10 had both typical angina and electrocardiographic evidence of myocardial ischemia during exercise. Four had left anterior hemiblock, 2 had left posterior hemiblock, 2 had right bundle branch block, 1 had right bundle branch block and left axis deviation, and 1 had left anterior hemiblock progressing to complete left bundle branch block. Cardiac catheterization revealed significant obstruction of the proximal left anterior descending coronary artery in all patients. Eight patients were treated surgically and 2 medically, all with relief of symptoms. Nine patients had repeat exercise stress testing, all without angina or electrocardiographic evidence of ischemia and all without recurrence of the conduction disturbance. The development of intraventricular conduction disturbances with ischemia during exercise testing strongly suggests disease of the proximal left anterior descending coronary artery.

VALVULAR HEART DISEASE

1103 Determinants of the Incidence and Severity of Ventricular Arrhythmias in Aortic Valve Disease

KLAUS V. OLSHAUSEN, FRANZ SCHWARZ, JÖRG APFELBACH, NORBERT RÖHRIG, BURKHARDT KRÄMER, and WOLFGANG KÜBLER, *With the technical assistance of* SONJA GUND

Twenty-four hour ambulatory electrocardiographic recordings in 93 patients with aortic valve disease revealed a high prevalence of ventricular arrhythmias. Only 16% of all patients had no ventricular premature beats (VPB), whereas multiform VPB were found in 47 patients (51%). Paired VPB were found in 32 (34%) and ventricular tachycardia in 17 (18%) of the 93 patients studied. The occurrence of ventricular arrhythmias was not related

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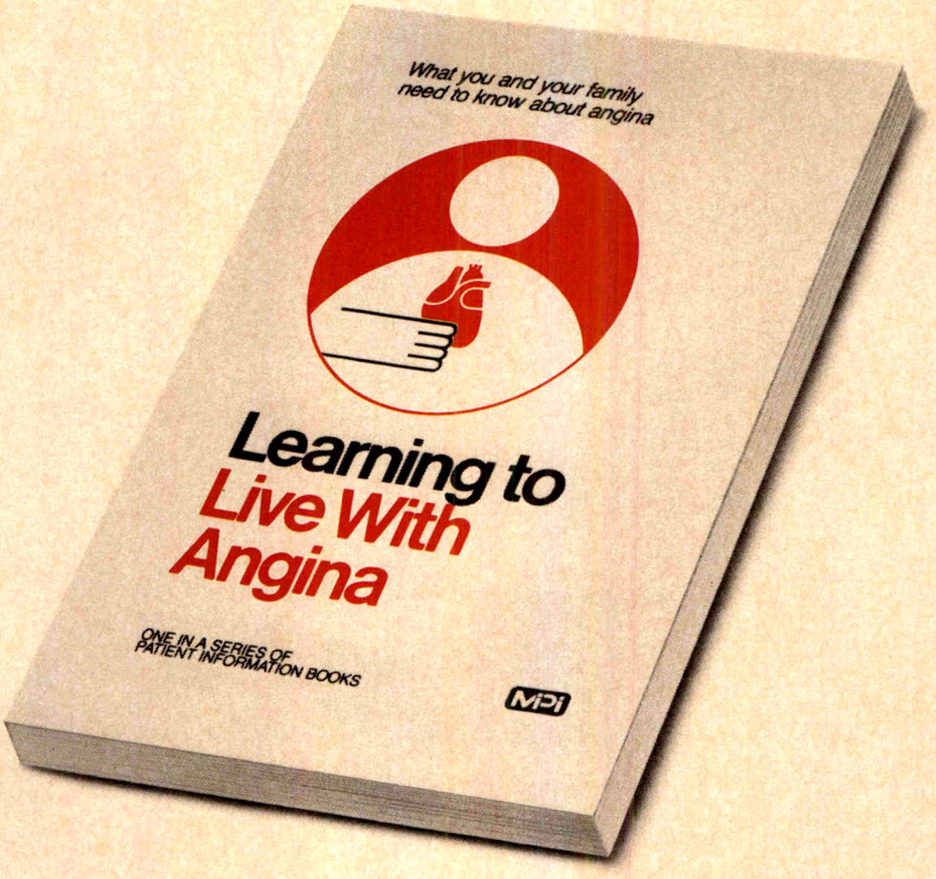

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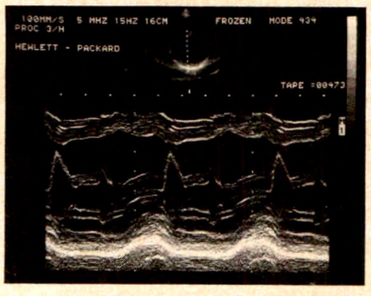

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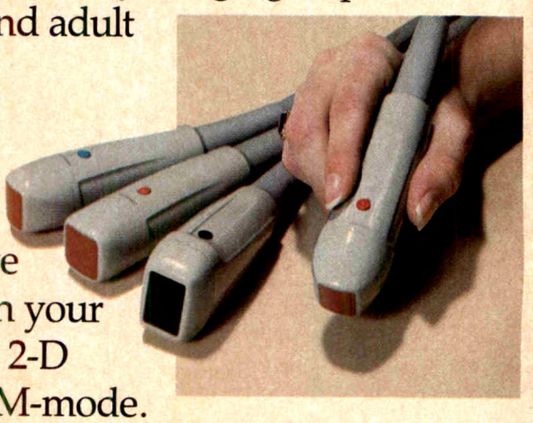

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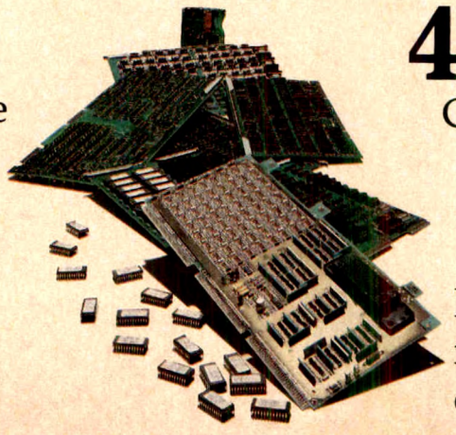

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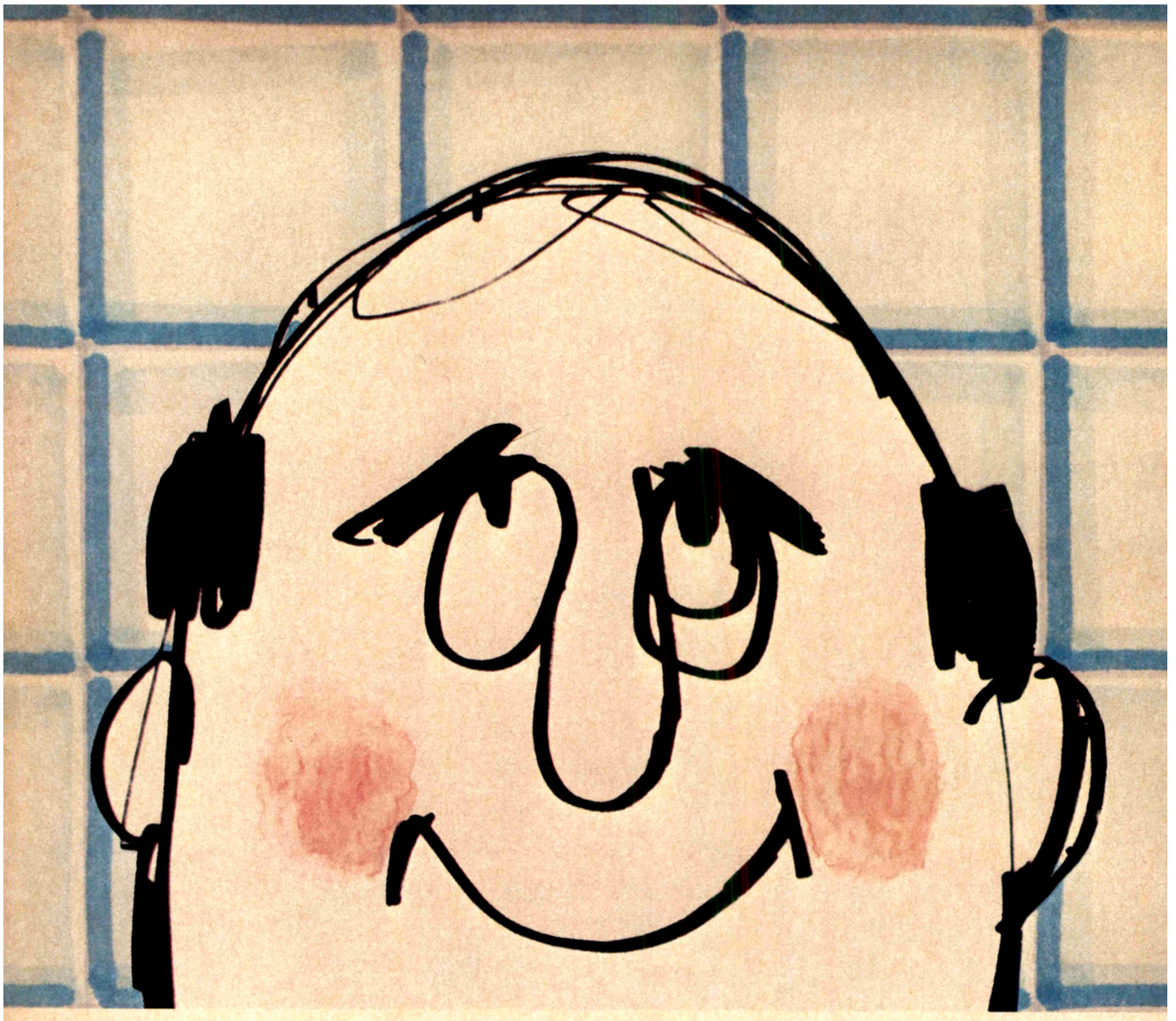

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to the type of valve lesion, to the transvalvular gradient in patients with aortic stenosis, or to the degree of regurgitation in patients with aortic insufficiency. The most important determinants of the incidence and severity of ventricular arrhythmias were a reduced left ventricular ejection fraction and an elevated peak systolic left ventricular wall stress. Thus, severe ventricular arrhythmias are frequently a sign of impaired left ventricular function.

1110 Left Ventricular Response to Isometric Exercise and Its Value in Predicting the Change in Ventricular Function After Mitral Valve Replacement for Mitral Regurgitation

HEIKKI V. HUIKURI, MARKKU J. IKÄHEIMO, MARKKU M. K. LINNALUOTO, and JUHA T. TAKKUNEN

Reduced left ventricular (LV) afterload and its consequent effect on the resting ejection fraction may lead to overestimation of LV function in mitral regurgitation (MR). To evaluate LV function during increased afterload of the heart, an isometric handgrip test was performed during cardiac catheterization in 15 patients with MR and 9 normal subjects. Twelve months after successful mitral valve replacement, the patients were recatheterized, and the value of preoperative stress test in predicting the change in resting ventricular function was estimated. Isometric exercise caused an increase in end-systolic wall stress, a measure of ventricular afterload, in both the MR group and the control group. The ejection fraction remained unchanged in the control group, but it decreased significantly in the MR group during exercise. A positive correlation existed between the change in ejection fraction during the preoperative stress test and the change in resting ejection fraction after mitral valve replacement. In conclusion, the isometric exercise-induced change in LV function appears to predict the influence of mitral valve replacement on LV function.

1116 Preoperative Invasive Testing in Mitral Stenosis: Indications Based on Assessment of Diagnostic Yield

MARC K. EFFRON, EDWIN L. ALDERMAN, and RICHARD L. POPP

The role of preoperative invasive testing in mitral stenosis was assessed in 82 patients undergoing cardiac catheterization for isolated mitral stenosis. The patients were diagnosed by physical examination and echocardiography, lacked clinical evidence of aortic valvular or coronary artery disease, and were considered for surgical treatment primarily to relieve dyspnea. All 38 patients in New York Heart Association functional class III and 8 of 9 patients in class IV had hemodynamic confirmation of mitral disease warranting operation. An operation was not recommended in 9 (26%) of 35 patients in class II who had normal or mildly abnormal pulmonary arterial wedge pressure. Coronary arteriography was performed in 44 patients (54%) and identified 4 patients with luminal narrowing >70%. These results suggest that preoperative invasive testing in patients with mitral stenosis is unnecessary when symptoms are moderate to severe. However, preoperative cardiac catheterization is indicated in patients with mild symptoms to prevent unnecessary or premature mitral operation.

1122 Noninvasive Diagnosis of Aortic and Mitral Valve Disease With Pulsed-Doppler Spectral Analysis

KENT L. RICHARDS, SCOTT R. CANNON, MICHAEL H. CRAWFORD, and SHERMAN G. SORENSEN

To differentiate normal from abnormal left-sided heart valves, 34 adults with 48 valve lesions proven at catheterization were examined using a 3 MHz duplex pulsed Doppler echocardiograph with 2-dimensional verification of sample volume position and on-line display of the Doppler audio spectrum. Intracardiac blood turbulence was the noninvasive indicator of disease. The specific lesion present was determined by documentation of the intracardiac location and timing of turbulence. Except for a single patient with minimal aortic regurgitation, Doppler spectral envelope areas in all normal valve sites were smaller than those measured at the same sites in the patients with aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation ($p < 0.01$). High sensitivity (97%) and specificity (100%) were noted despite the presence of multiple valve lesions in 67% of the patients. The data demonstrate application of a simple, noninvasive method of acquiring and analyzing Doppler echocardiographic data which allows accurate identification or exclusion of left-sided valve disease in adults, even in the presence of multiple valve lesions.

1128 Long-Term Results of Tricuspid Valve Replacement and the Problem of Prosthetic Valve Thrombosis

CHARLES W. THORBURN, JOHN J. MORGAN, MARK X. SHANAHAN, and VICTOR P. CHANG

Seventy-one patients had tricuspid valve replacement with Starr-Edwards, Björk-Shiley, Lillehei-Kaster, or porcine xenografts over a 14-year period. Prosthetic valve thrombosis occurred in 9 patients and was significantly more common with the tilting disc valves (20%) than with the Starr-Edwards valve (4%) ($p < 0.05$). Symptoms of thrombosis were often insidious, and presentation was therefore delayed. Streptokinase therapy relieved the obstruction in 1 of 2 patients.

Continued on Page A49

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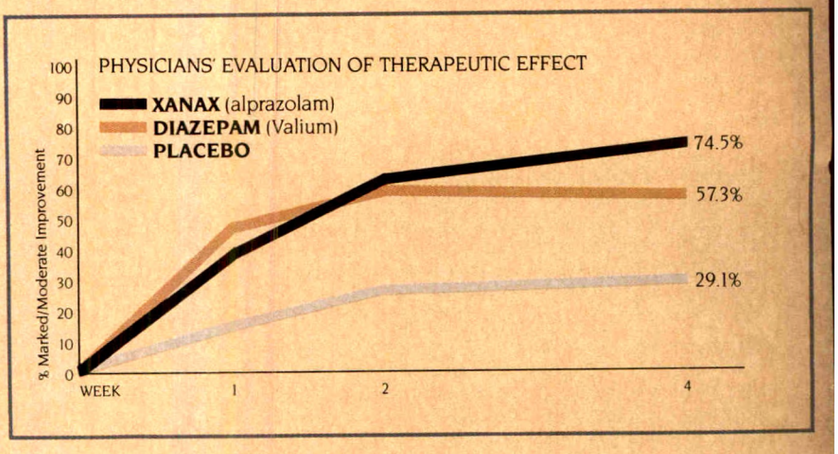

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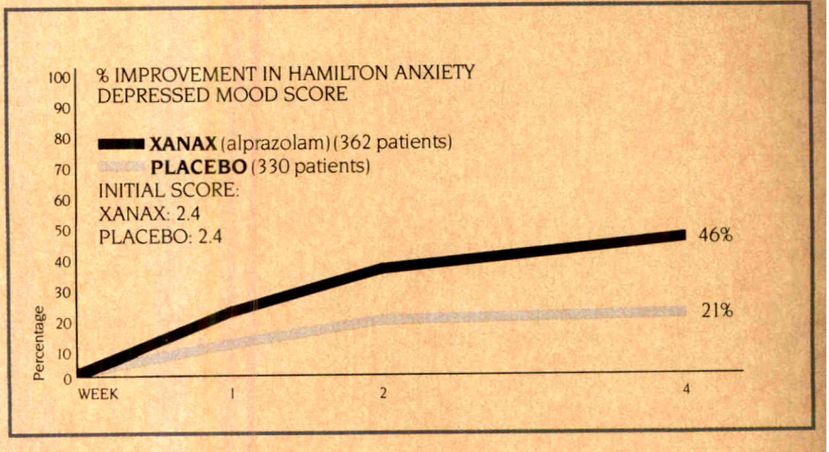
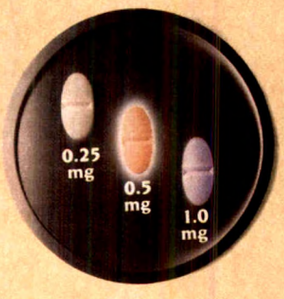


SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.



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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

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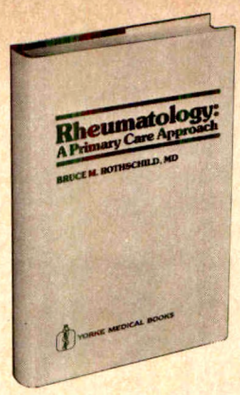
J-9554 May 1982



The Diagnosis and Treatment Oriented Approach to Rheumatology with the Primary Care Physician in Mind

Rheumatology

A Primary Care Approach

Written by:
Bruce M. Rothschild, MD
Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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CONGENITAL HEART DISEASE

1133 Symptomatic Sick Sinus Syndrome in Children and Adolescents as the Only Manifestation of Cardiac Abnormality or Associated With Unoperated Congenital Heart Disease

STANLEY D. BEDER, PAUL C. GILLETTE, ARTHUR GARSON, Jr., CO-BURN J. PORTER, and DAN G. McNAMARA

Sick sinus syndrome occurs infrequently in children who have not undergone cardiac surgery. The symptoms, electrocardiograms, and electrophysiologic data in 11 patients aged 2 to 17 years who had nonsurgical sick sinus syndrome were reviewed. Syncope and sinus bradycardia were common presentations. Sinus nodal recovery times and atrial and atrioventricular nodal refractory periods were measured. Abnormalities of atrial and atrioventricular nodal function were demonstrated in addition to sinoatrial nodal dysfunction. Therapeutic decisions in the management of patients with symptomatic sinus nodal dysfunction should reflect these associated electrophysiologic abnormalities when they are present.

1137 Sustained Ventricular Tachycardia After Repair of Tetralogy of Fallot: New Electrophysiologic Findings

JOHN D. KUGLER, WILLIAM W. PINSKY, JOHN P. CHEATHAM, PHILIP J. HOFSCHIRE, PAUL K. MOORING, and WILLIAM H. FLEMING

Ventricular arrhythmia originating from the outflow tract of the right ventricle is a presumed cause of late sudden death in patients after repair of tetralogy of Fallot. Exercise testing has been shown to enhance detection, and phenytoin has been shown to control ventricular arrhythmias in these patients. This study reports new findings in 3 patients who underwent electrophysiologic studies at postoperative cardiac catheterization; in each, sustained ventricular tachycardia was induced and found to originate from the inflow-septal area of the right ventricle. Using serial studies, the same sustained ventricular tachycardia was induced during therapeutic serum concentrations of phenytoin but not after propranolol. No patient had ventricular arrhythmia during a 24-hour electrocardiogram or during exercise. Although no patient had normal hemodynamic function, only 1 patient had right ventricular pressure greater than two-thirds systemic pressure. Each patient had undergone initial intracardiac repair at a relatively late age (3, 9, and 9 years).

1144 Right Ventricular Function in Adults With Pulmonary Hypertension With and Without Atrial Septal Defect

MARVIN A. KONSTAM, JOHN IDOINE, JOSHUA WYNNE, WILLIAM GROSSMAN, LAWRENCE COHN, J. ROBERT BECK, JOSEPH KOZLOWSKI, and B. LEONARD HOLMAN

This study examined right ventricular (RV) function in 22 patients with pulmonary hypertension, and assessed the influence of a left-to-right shunt on systolic performance. In patients with pulmonary hypertension without volume overload (group I), RV ejection fractions, measured by radionuclide ventriculography (mean 0.35 $\pm$ 0.11) were significantly lower than in normal control subjects. In 8 patients (group II) with RV systolic pressures similar to those in group I, but with atrial-level left-to-right shunts, RV ejection fractions were normal and significantly higher than in group I. RV end-diastolic volumes were significantly greater in group II than in group I. RV ejection fractions decreased significantly in 5 patients after isolated atrial septal defect repair. The findings indicate that in patients with RV volume overload due to atrial septal defect, systolic function, measured by ejection fraction, remains normal despite pulmonary hypertension, and decreases after surgical reduction in preload.

1149 The Univentricular Heart: Combined 2-Dimensional-Pulsed Doppler (Duplex) Echocardiographic Evaluation

GEORGE S. BISSET, III and STEPHEN S. HIRSCHFELD

The combination of 2-dimensional echocardiography and pulsed Doppler echocardiography (2D/PD) has provided an extremely useful noninvasive tool in pediatric cardiology. Fourteen children with univentricular hearts were evaluated with this technique in an attempt to delineate specific morphologic and functional characteristics. Ventricular and atrial morphology, atrioventricular valve connections, and great vessel positions were accurately identified. Information concerning aortic and pulmonary flow patterns, atrioventricular valve competence, and shunt patterns could also be obtained. In several of the patients, 2D-PD evaluation provided more anatomic and functional information than angiography. It is concluded that the use of 2-dimensional echocardiography coupled with a range-gated Doppler system will improve recognition of patients with univentricular hearts and permit thorough evaluation of specific anatomic details.

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1155 Prognostic Value of Left Ventricular Size Measured by Echocardiography in Infants With Total Anomalous Pulmonary Venous Drainage

CARLOS OLIVEIRA LIMA, LILLIAM M. VALDES-CRUZ, HUGH D. ALLEN, SUZANA HOROWITZ, DAVID J. SAHN, STANLEY J. GOLDBERG, JESUS VARGAS BARRON, and EHUD GRENADIER

Left ventricular (LV) size may be a determinant of survival in infants with total anomalous pulmonary venous drainage (TAPVD). Right (RV) and LV size were measured by M-mode and 2-dimensional (2-D) echocardiography in 13 patients aged 1 day to 4 months who underwent surgery before age 4 months because of severe cyanosis or cardiac failure. Seven patients had venous drainage to a vertical vein; 4 had drainage to the right atrium and 2 had drainage to the inferior vena cava. Patients were divided into 2 groups: survivors (Group A, n = 8) and nonsurvivors (Group B, n = 5). Death was not statistically related to pulmonary artery pressure, pulmonary venous obstruction, age, or weight at time of surgery. RV and LV sizes at end-diastole measured from M-mode traces and 2-D echocardiographic 4-chamber views were compared with those from 15 weight-matched control infants. On M-mode and 2-D echocardiography, nonsurvivors had significantly larger RV and smaller LV dimensions than either controls or surviving TAPVD patients. The ratio of RV/LV size on M-mode and 2-D echocardiography was also different in the 3 infant groups ($p < 0.001$). RV/LV size separated nonsurvivors from survivors and controls. Postmortem examinations available in 4 of the 5 nonsurvivors demonstrated that the ratio of RV/LV size in the specimens closely agreed with the 2-D echocardiographic ratios. Our study agrees with the impression of other investigators that LV size may be a determinant of survival after repair of TAPVD.

CARDIOMYOPATHY

1160 Hypertrophic Obstructive Cardiomyopathy: Ten-to-21 Year Follow-Up After Partial Septal Myectomy

MARGARET M. BEAHRS, ABDUL J. TAJIK, JAMES B. SEAWARD, EMILIO R. GIULIANI, and DWIGHT C. McGOON

This study reviews the outcome in 36 consecutive patients who survived partial septal myectomy for hypertropic obstructive cardiomyopathy (operated on between 1960 and 1972). All patients were followed up until death or until June 1981 (mean follow-up 13.4 years). Of the 26 survivors, 17 had been more than mildly symptomatic preoperatively, but only 1 remained so postoperatively. The operation was effective in relieving the obstruction (average peak systolic gradient reduced from 79 to 8 mm Hg [$p < 0.001$]), and mitral regurgitation was relieved. No surviving patient's symptoms worsened, but 10 patients died late (4 suddenly, 5 from congestive heart failure, and 1 from a neoplasm). The 10-year survival rate was 77%. These results suggest a favorable effect of operation and support continued surgical intervention for appropriate patients.

1167 Clinical and Morphologic Cardiac Findings After Anthracycline Chemotherapy. Analysis of 64 Patients Studied at Necropsy

JEFFREY M. ISNER, VICTOR J. FERRANS, STEVEN R. COHEN, BRUCE G. WITKIND, RENU VIRMANI, JOHN S. GOTTDIENER, J. ROBERT BECK, and WILLIAM C. ROBERTS

The relation between clinical evidence of and histologic signs of anthracycline cardiotoxicity was evaluated by reviewing the clinical and morphologic findings in 64 patients studied at necropsy, all of whom had received Adriamycin or Daunomycin chemotherapy during life. In 7 (35%) of 20 patients with documented clinical toxicity consisting of impaired left ventricular systolic performance, histologic signs of cardiotoxicity were absent. Of 44 patients without clinical signs of toxicity, morphologic signs of cardiotoxicity were present in 23 (52%), mild in most patients but extensive in 4. The results of this study raise serious questions regarding the reliability of endomyocardial biopsy to monitor cardiotoxicity in patients undergoing anthracycline chemotherapy.

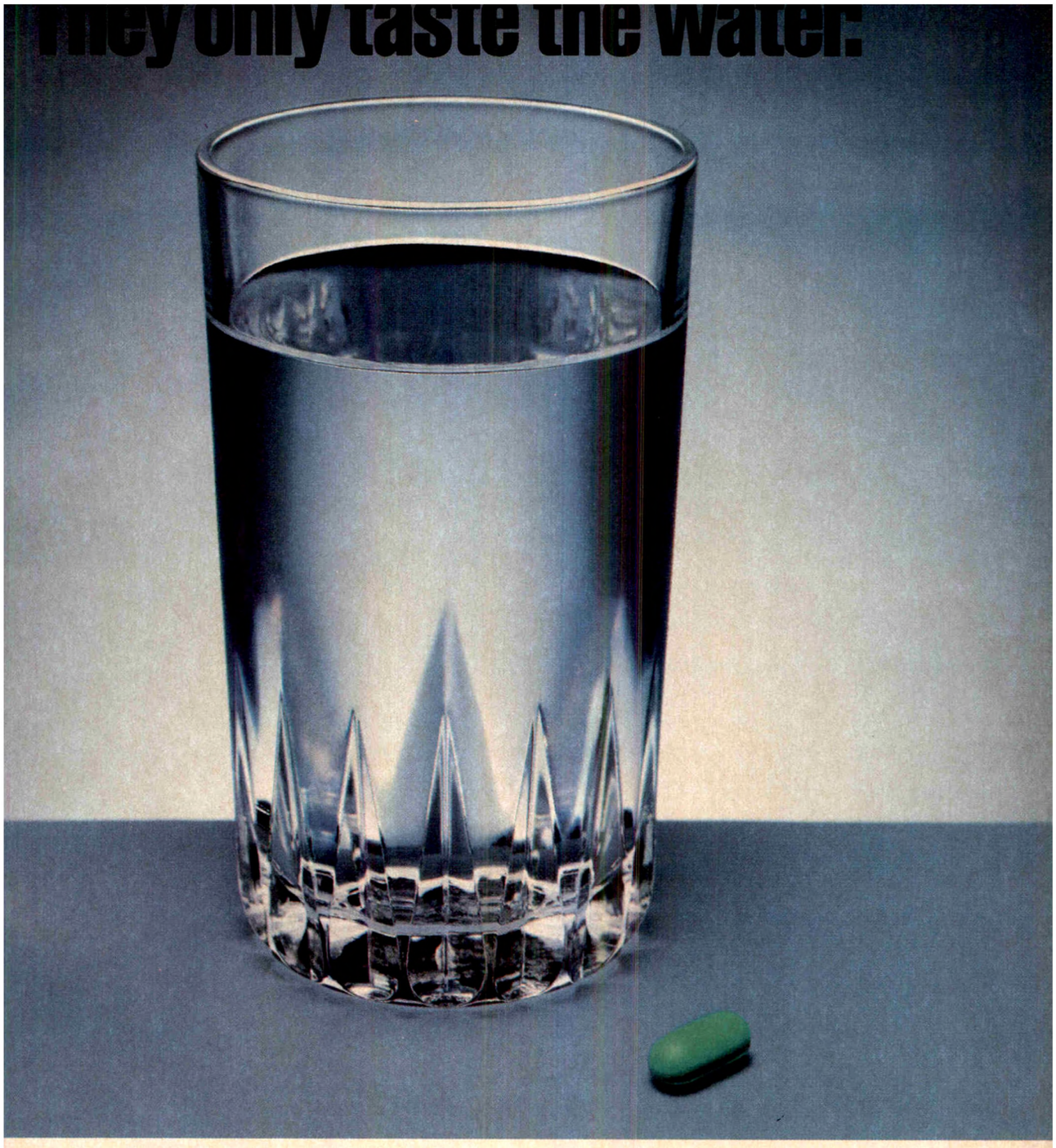
ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1175 Mexiletine for Control of Drug-Resistant Ventricular Tachycardia. Clinical and Electrophysiologic Results in 44 Patients

LAWRENCE E. WASPE, HARVEY L. WAXMAN, ALFRED E. BUXTON, and MARK E. JOSEPHSON

This study evaluated the antiarrhythmic efficacy of mexiletine in 44 patients with recurrent drug-resistant ventricular tachyarrhythmias. Electrophysiologic testing on mexiletine alone or in combination with conventional drugs was performed in 33 patients, all of whom had inducible ventricular tachycardia (VT) during control studies. VT remained inducible with methods similar to control inductions in 25 of these patients. Only 8 patients (24%) had no inducible ventricular tachyarrhythmia on mexiletine (3) or mexiletine combined with another drug (5). Mexiletine alone or in combination with another agent suppressed VT recurrences in 5 of 11 additional pa-

Continued on Page A55



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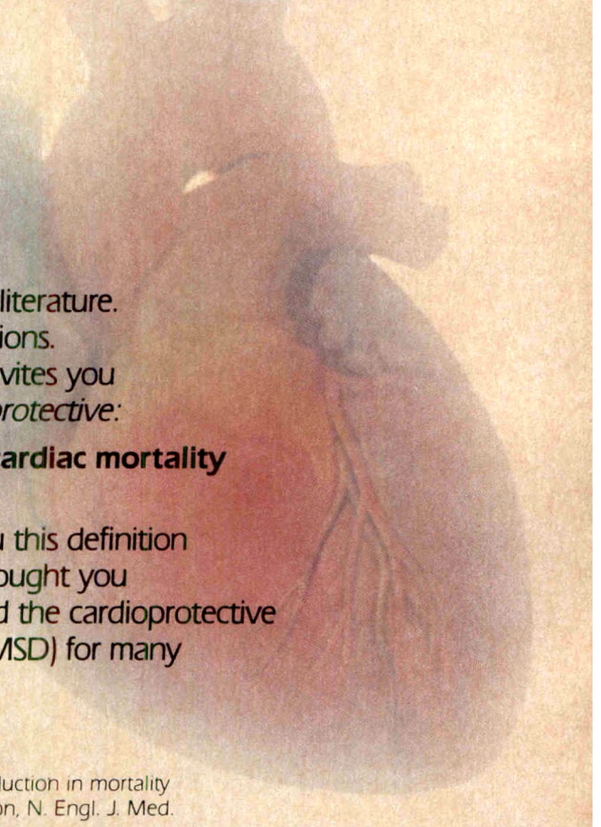

Cardioprotective is a word you won't find in standard medical dictionaries.

But you will find it appearing in the medical literature. And you will be hearing it in medical discussions. Until dictionaries recognize the term, MSD invites you to use this as a working definition of *cardioprotective:*

"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrup Withdrawal—Hypersensitivity to catecholamines has bee observed in patients withdrawn from beta-blocker therap exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administere timolol maleate, particularly in patients with ischemic hea

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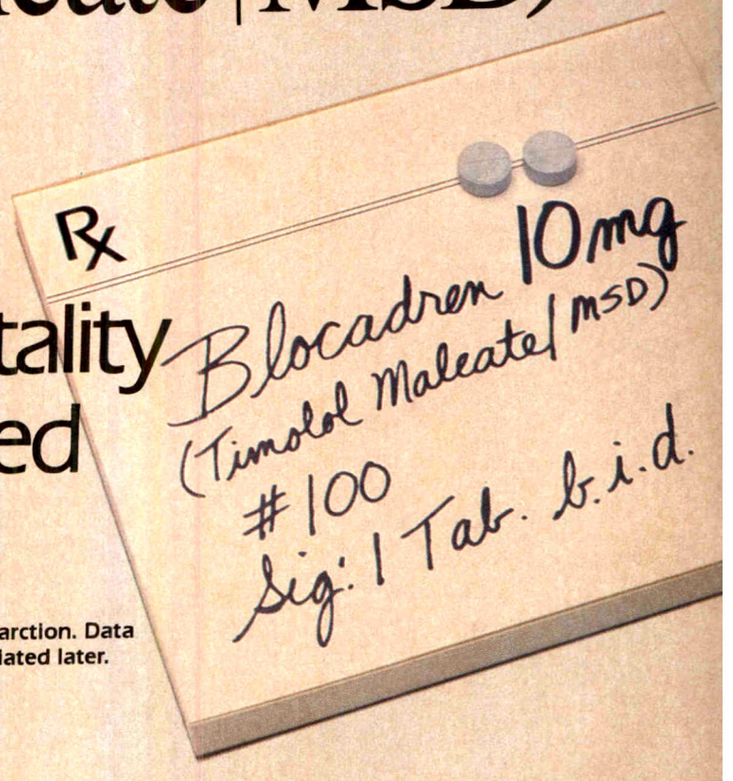
Timolol Maleate (MSD)

reduces the risk of reinfarction and cardiac mortality for many stabilized post-MI patients



Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.

disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

BLOCADREN®
(TIMOLOL MALEATE | MSD)

CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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tients who did not undergo programmed stimulation. These 5 patients and the 8 patients with no inducible arrhythmia were discharged on mexiletine alone (5) or in combination with other drugs (8), and remained free of arrhythmia recurrences for a mean of 7.7 months. Adverse effects occurred in 61% of patients, and caused discontinuation of the drug in 6 patients (14%). Therefore, mexiletine alone had limited antiarrhythmic efficacy, but when combined with conventional drugs, was of some utility in 13 of 44 patients (30%). Adverse effects were frequent, and constituted a further limitation to the usefulness of mexiletine.

1182 Possible Contribution of Encainide Metabolites to the Long-Term Antiarrhythmic Efficacy of Encainide

ROGER A. WINKLE, FLORA PETERS, ROBERT E. KATES, and DONALD C. HARRISON

Twelve patients with frequent premature ventricular contractions underwent 1 year of therapy with encainide. Average suppression of premature ventricular contractions ranged from 97 to 99%. The plasma concentration of encainide metabolites exceeded that of encainide by several-fold during chronic dosing. When encainide was withdrawn at 6 and 12 months, arrhythmias did not return in many patients until well after encainide levels were undetectable. At the time of arrhythmia return considerable levels of encainide metabolites were still present in the plasma, raising the possibility that these metabolites were contributing to the drug's antiarrhythmic effect.

1189 Beat-to-Beat Left Ventricular Performance in Atrial Fibrillation: Radionuclide Assessment With the Computerized Nuclear Probe

JAMES SCHNEIDER, HARVEY J. BERGER, MILTON J. SANDS, ANTHONY B. LACHMAN, and BARRY L. ZARET

Left ventricular (LV) ejection fraction and relative LV volumes were evaluated on a beat-to-beat basis with the computerized nuclear probe, an instrument with sufficiently high sensitivity to allow continuous evaluation of the radionuclide time-activity curve. Consecutive beats were analyzed in each of 18 patients. The mean LV ejection fraction was 17 to 51%. There was substantial beat-to-beat variation in cycle length and LV ejection fraction in all patients, including those with marked LV dysfunction. There was an excellent correlation between mean ejection fraction derived from the nuclear probe and gated ejection fraction obtained by gamma camera imaging ($r = 0.91$). Based on beat-to-beat analysis, LV function was dependent on relative end-diastolic volume and multiple preceding cycle lengths, but not preceding end-systolic volumes. This study demonstrates that a single value for LV ejection fraction does not adequately characterize LV function in atrial fibrillation.

1196 Comparative Effects of Beta-Adrenergic Blocking Drugs on Experimental Ventricular Fibrillation Threshold

JEFFREY L. ANDERSON, HUGO E. RODIER, and LARRY S. GREEN

Clinical studies have suggested that certain beta-blocking agents may reduce sudden death in postinfarction patients, but the mechanism is unknown. In this study, canine ventricular fibrillation thresholds were measured before and after intravenous administration of various doses of representative beta-blocking drugs or saline solution. Thresholds were also determined 3 minutes after ligation of the mid-anterior descending coronary artery. Significant increases in ventricular fibrillation thresholds occurred, both with and without ischemia, with each beta-blocker tested, averaging up to 6-fold. However, the minimal effective doses at which maximum effects occurred varied widely, in the following order: timolol >pindolol >propranolol ≥metoprolol >labetolol. Beta-blocking potencies thus were better predictors of relative antifibrillatory potencies than were individual accessory drug properties. Interruption of cardiac sympathetic stimulation was shown to account for part of the antifibrillatory effect. Elevation in ventricular fibrillation threshold may be an important mechanism by which beta-blockers reduced cardiac mortality in ischemic heart disease.

1203 Effects of Exercise and Isoproterenol During Atrial Fibrillation in Patients With Wolff-Parkinson-White Syndrome

LAWRENCE D. GERMAN, JOHN J. GALLAGHER, ARCHER BROUGHTON, TOM GUARNIERI, and JOEY L. TRANTHAM

Exercise and isoproterenol infusion were studied during atrial fibrillation in 17 patients with Wolff-Parkinson-White syndrome to assess their effects on conduction over the accessory atrioventricular connection. Exercise favored conduction over the atrioventricular node and resulted in a lesser degree of preexcitation. Isoproterenol allowed rapid ventricular responses to be achieved in some patients not previously demonstrating rapid conduction over the accessory pathway. This study demonstrates the usefulness of isoproterenol infusion in patients with Wolff-Parkinson-White syndrome for assessing the risk of developing rapid ventricular rates during atrial fibrillation.

Continued on Page A59

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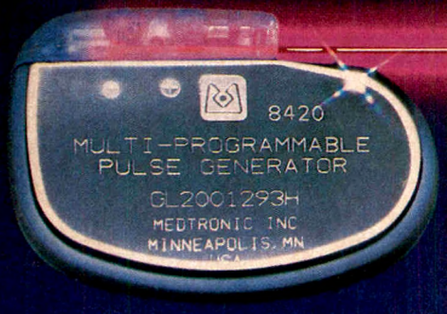

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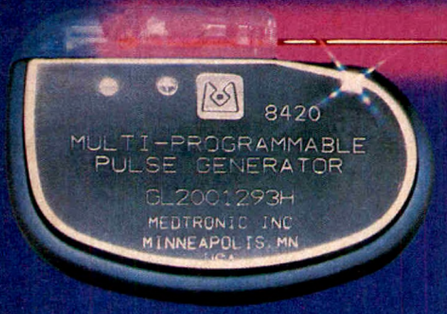

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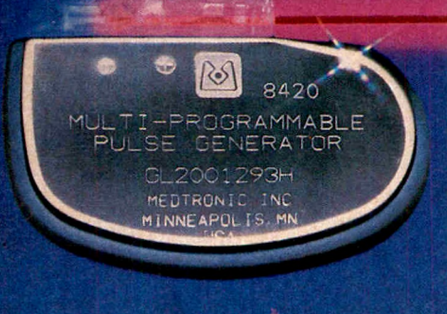

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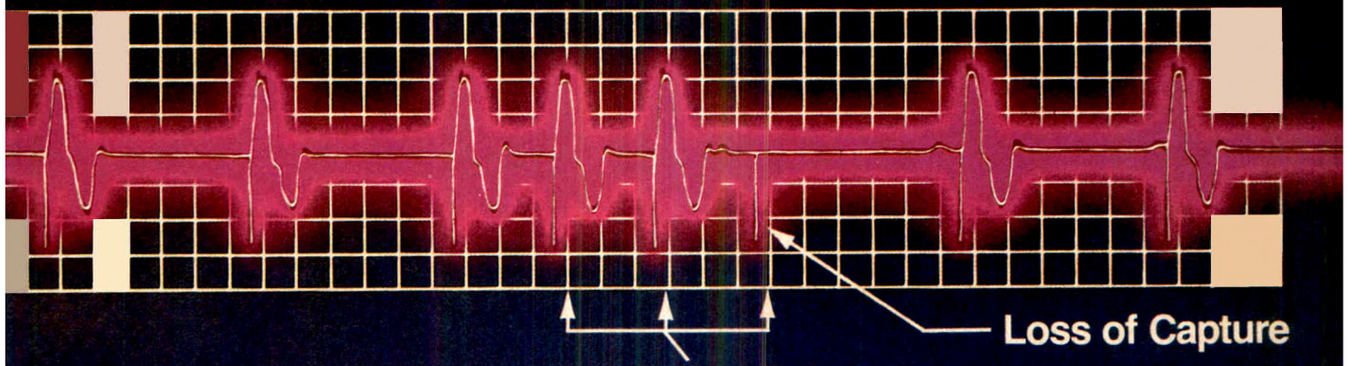

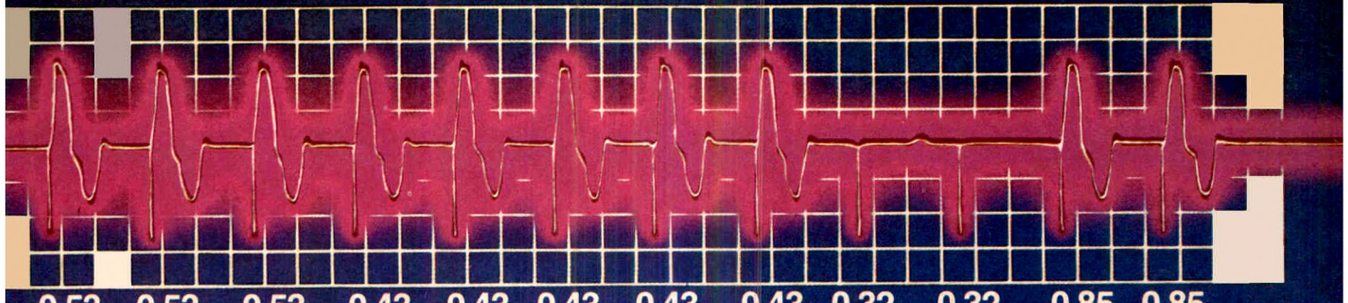

Stimulus Pulse Width (MS)

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SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
*    BATTERY OK     *
*        RATE= 70PPM*
*          PW=0.50MS*
*       SENSE= 2.5MV*
*        AMPL=FULL  *
*        HYST=NONE  *
*MAGNET ASYNC MODE *
*        REFR=325MS *
*PERM    DEMAND MODE*
```

```
SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
ELECT. REPLACE TIME!
*        RATE= 70PPM*
*          PW=0.50MS*
*       SENSE= 2.5MV*
*        AMPL=FULL  *
*        HYST=NONE  *
*MAGNET ASYNC MODE *
*        REFR=325MS *
*PERM    DEMAND MODE*
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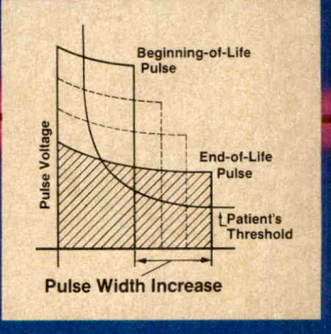

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Medtronic Implantable Pulse Generators and Leads

Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

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MISCELLANEOUS TOPICS

1207 Prevalence and Correlates of Posterior Extra Echocardiographic Spaces in a Free-Living Population Based Sample: The Framingham Study

DANIEL D. SAVAGE, ROBERT J. GARRISON, FREDERICK BRAND, SANDRA J. ANDERSON, WILLIAM P. CASTELLI, WILLIAM B. KANNEL, and MANNING FEINLEIB

To obtain epidemiologic information on extra echocardiographic spaces immediately posterior to the left ventricular free wall, 2,028 subjects in the original Framingham cohort study (mean age 70 ± 7 years) and 3,624 of the offspring of the cohort (and their spouses) (mean age 44 ± 10) with adequate echocardiograms were evaluated. Extra echocardiographic spaces were detected in 370 (6.5%) of the 5,652 subjects. The prevalence ranged from <1% in subjects in the 20- to 30-year age decade to >15% for those in their 80s. Extra echocardiographic spaces tended to be more common in subjects who were older, female, obese, and more hypertensive, and those who had higher blood sugar and higher low density lipoprotein cholesterol levels (measured 8 years earlier). Extra echocardiographic spaces were significantly and independently associated with age and obesity in multivariate analysis. The possibility that such extra echocardiographic spaces may often represent subepicardial fat rather than pericardial fluid deserves further study.

1213 Effect of Verapamil on Left Ventricular Function: A Randomized, Placebo-Controlled Study

RONALD E. VLIETSTRA, MARIA A. C. FARIAS, ROBERT L. FRYE, HUGH C. SMITH, and ERIK L. RITMAN

The effects of verapamil on left ventricular function were tested in 25 patients with suspected coronary artery disease. A double-blind, randomized, placebo-controlled study design was used. Verapamil (0.2 mg/kg over 10 minutes) significantly lowered mean arterial pressure while increasing the cardiac index. No statistically significant effect was seen on heart rate, left ventricular end-diastolic pressure or end-systolic volume index, ejection fraction, peak rates of systolic wall thickening or diastolic wall thinning, or percentage of hemiaxial shortening. However, there was a small increase in the left ventricular end-diastolic volume index. The study demonstrates that verapamil acutely reduces systemic vascular resistance, increases left ventricular end-diastolic volume index (consistent with a negative inotropic effect), and does not appear to improve regional wall dynamics in portions of the left ventricular wall considered hypokinetic because of myocardial ischemia.

1218 Hemodynamic and Electrocardiographic Effects in Man of a New Nonionic Contrast Agent (Iohexol): Advantages Over Standard Ionic Agents

G. B. JOHN MANCINI, J. NEUKAM BLOOMQUIST, VALMIK BHARGAVA, JOSEPH B. STEIN, WILBUR LEW, ROBERT A. SLUTSKY, RALPH SHABETAI, and CHARLES B. HIGGINS

Iohexol is a new, nonionic contrast material that has been shown in animal studies to hold great promise as an agent for coronary arteriography and ventriculography with fewer adverse effects than standard ionic media. It has not yet been systematically studied in man. Fifty patients referred for elective cardiac catheterization were randomized to receive either iohexol or meglumine sodium diatrizoate (Renografin®-76). Hemodynamic and electrocardiographic measurements were made after left ventriculography and both left and right coronary arteriography. Iohexol produced fewer deleterious hemodynamic and electrocardiographic changes. This favorable preliminary experience in man has potential clinical importance because of the large number of patients undergoing angiographic procedures.

1223 Increased Left Ventricular Function as an Adaptive Response in Vibration Disease

TSUNETAKA MATOBA, MORIO ITAYA, KOJI TOYOMASU, TAKEYOSHI TSUIKI, HIRONORI TOSHIMA, and HIROSHI KUWAHARA

Left ventricular function was studied in 35 patients with vibration disease and 35 age-matched healthy subjects. The average age was 49 years. The left ventricular ejection fraction (EF) in vibration disease by the method of echocardiography was 89 ± 4%, which is significantly higher than in the control subjects ($p < 0.01$). EF tended to increase with the increases in the level of autonomic nerve activity. The stroke volume index in patients with vibration disease was also significantly larger than in the controls ($p < 0.001$). Electrocardiographically, the ratio of T waves to R waves in precordial leads was larger than in the controls. Resting heart rate in the vibration disease was significantly lower than in the controls ($p < 0.001$). These findings suggest that the cardiovascular system in vibration disease due to vibration, noise, and cold provides an adaptive response to the stressors.

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BRIEF REPORTS

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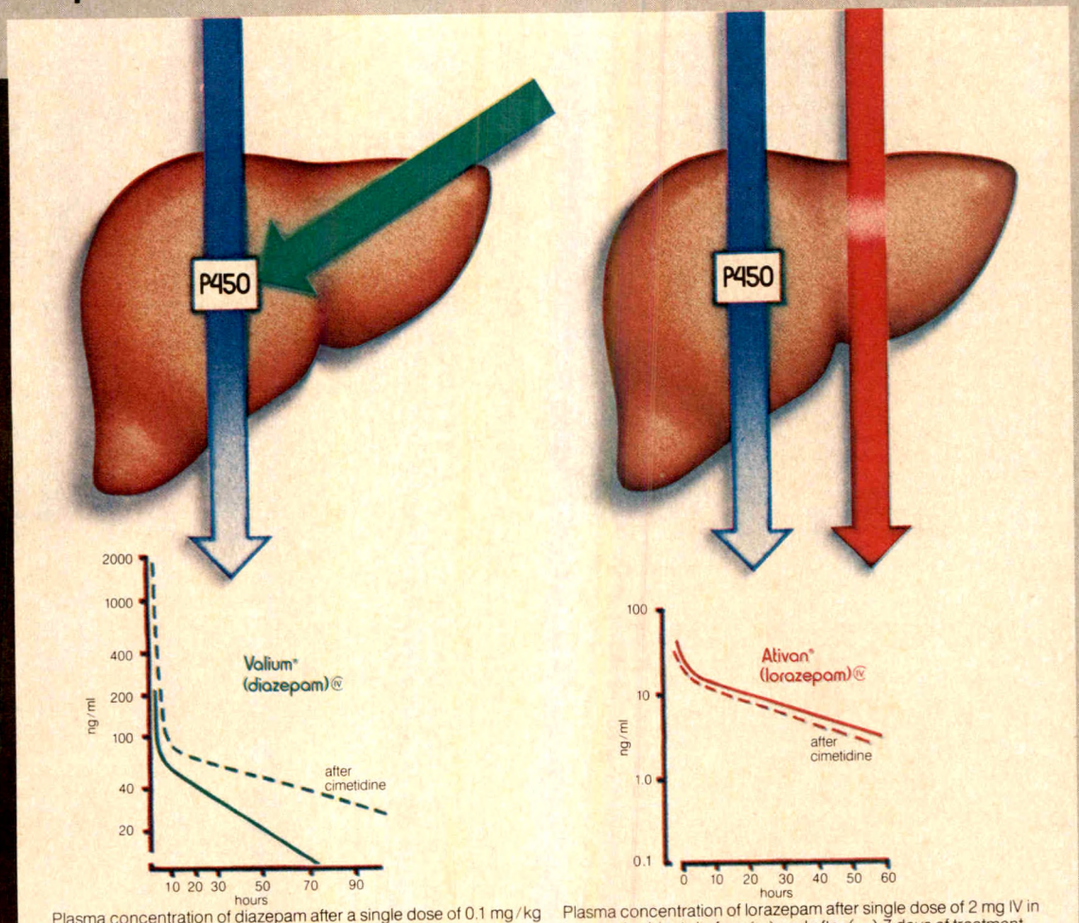
Ativan®: Agent of Change
(lorazepam)



Plasma concentration of diazepam after a single dose of 0.1 mg/kg IV to a single subject administered before (—) and after (---) pretreatment with cimetidine—5 X 200 mg orally q6h. (Adapted from Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.)

Plasma concentration of lorazepam after single dose of 2 mg IV in 8 normal subjects before (—) and after (---) 7 days of treatment with cimetidine, 300 mg orally qid. (Adapted from Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.)

because it doesn't utilize the P450 system

All drugs inactivated by oxidative metabolism, including cimetidine and most benzodiazepines, utilize the cytochrome P450 oxidase enzyme system and, therefore, compete for it when given concomitantly. Patients on cimetidine, for example, are apt to experience excessive drowsiness when taking a benzodiazepine dependent on this system—because benzodiazepine clearance is delayed and plasma levels increase.

Ativan® (lorazepam) is inactivated by simple, one-step glucuronidation and is not subject to N-dealkylation or hydroxylation by the P450 system—unlike diazepam, chlordiazepoxide, clorazepate and prazepam, all CIV.

And, since Ativan does not compete for the P450 system, its elimination is not appreciably affected by concomitant use of cimetidine... one more reason why Ativan is becoming the anxiolytic of choice for an increasing number of physicians.

See important information on following page.

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Wyeth Laboratories
Philadelphia, PA 19101

Ativan®
for (lorazepam)℞ IV
Anxiety

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NEW TABLET DESIGN 0.5 mg and 1 mg

(2 mg tablet retains original oval shape at present)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) for Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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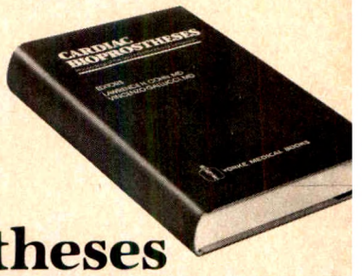

Cardiac Bioprostheses

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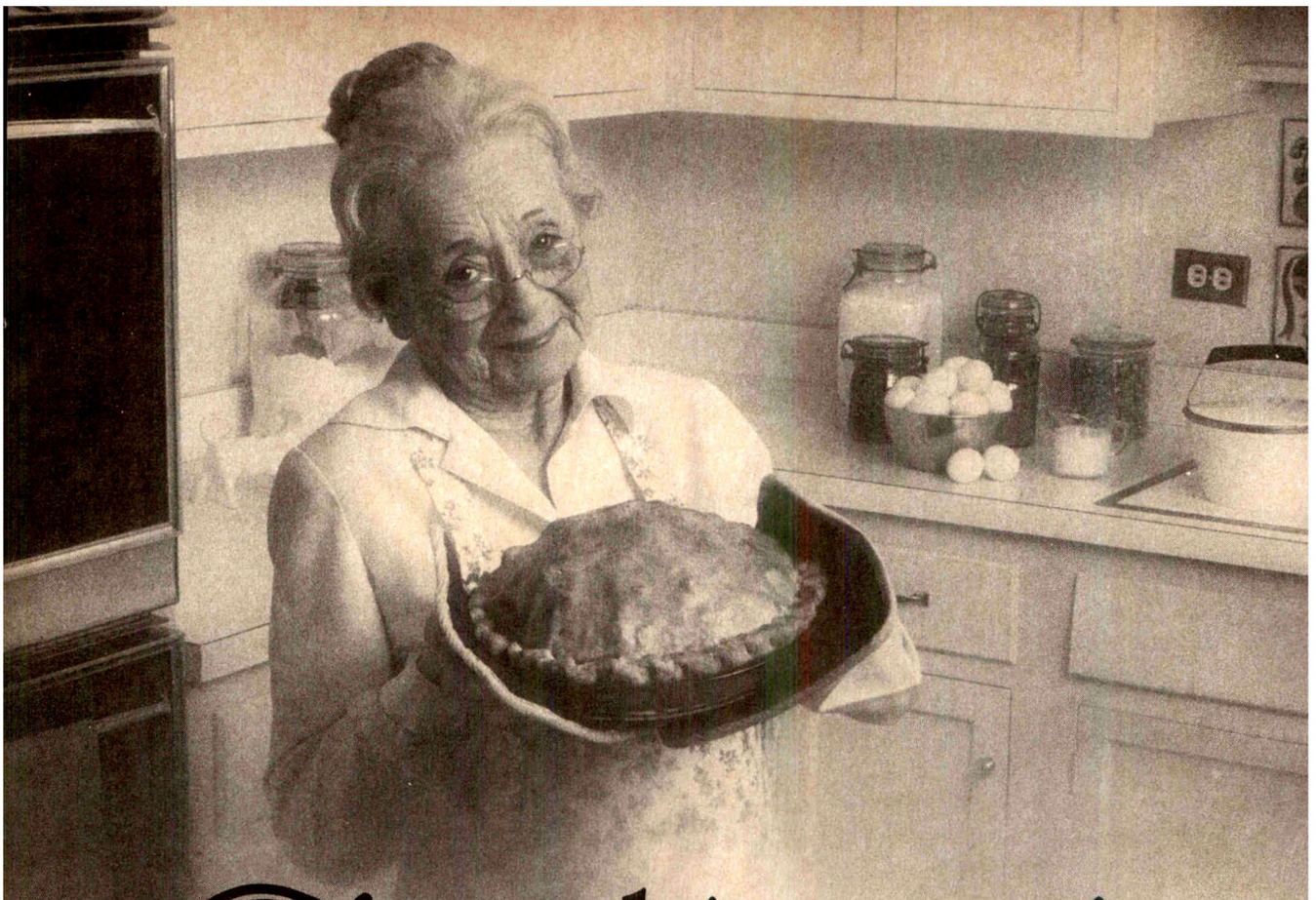

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Late Prognostic Value of Scintigraphic Parameters Of Acute Myocardial Infarction Size in Complicated Myocardial Infarction Without Heart Failure

ELIAS H. BOTVINICK, MD, JUAN F. PEREZ-GONZALEZ, MD, PhD, RICHARD DUNN, MD, THOMAS PORTS, MD, KANU CHATTERJEE, MD, and WILLIAM PARMLEY, MD

Perfusion scintigraphy with thallium-201, infarct scintigraphy with technetium-99m pyrophosphate (TcPYP), and equilibrium blood pool scintigraphy were performed during the initial hospitalization for acute myocardial infarction (MI) in 25 patients without evidence of heart failure who presented with advanced electrocardiographic rhythm and conduction disturbances requiring treatment. Scintigraphic findings during short-term hospitalization were related to the late clinical follow-up performed an average of 14 months later, where patients were grouped as asymptomatic, 8 patients; symptomatic, 9 patients; and deceased, 8 patients. Quantitation of perfusion abnormalities, TcPYP image abnormalities, and left ventricular ejection fraction (EF) revealed that the deceased group had significantly larger TcPYP abnormalities (36 ± 20 cm^2), absolute perfusion abnormalities (32 ± 16 cm^2), and perfusion abnormalities expressed as a percentage of the projected left ventricular area (42 ± 8%) than the asymptomatic group (13 ± 8 cm^2, 14 ± 6 cm^2, and 20 ± 9%; $p < 0.05$, $p > 0.05$, and $p < 0.01$, respectively). The percent perfusion abnormality was significantly larger in the deceased group (42 ± 8%, $p < 0.01$) than in either the symptomatic group (35 ± 13%, $p < 0.01$) or the asymptomatic group (20 ± 9%), and this parameter in the symptomatic group also differed from that in the asymptomatic group ($p < 0.01$).

The study indicates that patients with rhythm and conduction disturbances and without congestive heart failure during acute MI may follow an uncomplicated or a complicated late clinical course. Early scintigraphic measurements of MI and perfusion correlate well with this outcome; however, EF could not differentiate among prognostic subgroups.

Death during an acute myocardial infarct (MI) and prognosis after the event have been related to MI size.[1–3] Several noninvasive clinical and laboratory parameters, including precordial S-T segment mapping[4,5] and enzymatic measurements,[6,7] have met limited success as measures of acute MI size.[5,8] Scintigraphic parameters of acute MI size have been related to the location and extent of necrosis in both animals and man.[9,10] Recently, acute MI size, as assessed by technetium-99m pyrophosphate (TcPYP) scintigraphy,[11,12] perfusion scintigraphy,[13,14] and indirect scintigraphic parameters of left ventricular function, particularly ejection fraction [EF],[15] have been associated with both early and late prognosis after acute MI.

From the Department of Medicine, Division of Cardiology, the Department of Radiology, Section of Nuclear Medicine, and the Cardiovascular Research Institute of the University of California at San Francisco. This study was supported in part by Grant HL 21793 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, a grant from the Fannie Ripple Foundation, Morristown, New Jersey. Dr. Botvinick is supported in part by a Grant-in-Aid from the George D. Smith Foundation, San Francisco, California, and is a recipient of the American Heart Association Established Investigator Award. Dr. Dunn is a recipient of an Overseas Clinical Fellowship from the National Heart Foundation of Australia, Sydney, Australia. Manuscript received July 6, 1982; revised manuscript received December 21, 1982, accepted December 22, 1982.

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Among clinical parameters which have been related to prognosis after acute MI, disturbances of cardiac rhythm[16–18] and conduction[19,20] appear prominent. In addition, both rhythm and conduction disturbances are known contributors to sudden death[21] and are frequently related to heart failure, where the prognostic impact is compounded.[22] However, the late prognosis of patients with rhythm and conduction disturbances but without heart failure early after MI may be difficult to predict early. The purpose of this study was to determine whether scintigraphic measurements of acute MI size, perfusion abnormalities, and left ventricular function, measured early after the event, could be related to the late prognosis in such patients.

Methods

Patient population: From a larger group of 62 consecutive patients admitted to the coronary care unit with acute MI and studied prospectively with scintigraphic techniques, 25 patients were found to have rhythm and conduction disturbances in the absence of heart failure; they form the basis of this report. Patients with acute MI were included if, in the absence of symptoms or signs of heart failure, they presented with rhythm disturbances defined as ventricular fibrillation, ventricular tachycardia, complex premature ventricular contractions of Lown classification 3 or higher,[17] atrial fibrillation or flutter requiring treatment, and/or conduction disturbances, including second- and third-degree atrioventricular block requiring a pacemaker or bifascicular bundle branch block. There were 20 men and 5 women with a mean age of 61 years (range 37 to 88). As for the group as a whole, the diagnosis of acute MI in this subgroup was based on at least 2 of the following 3 criteria: (1) a history of typical prolonged chest pain; (2) electrocardiographic (ECG) changes indicative of myocardial injury including S-T depression ≥1.0 mm, T-wave inversion persisting for ≥24 hours, a newly developed QS complex or Q waves ≥0.04 second; (3) characteristic elevation of total creatine kinase to a peak level ≥90 IU/liter or MB component ≥4% of the total creatine kinase, or both. Serum enzyme determinations were performed on admission, then every 4 hours for 24 hours, and then every 6 hours to 72 hours. Creatine kinase was measured by a fluorometric method[23] and creatine kinase-MB by an electrofluoretic method.[24] Historical and ECG evidence of previous MI was sought.

Acute MI was diagnosed as transmural with the appearance of new QS complexes or Q waves ≥0.04 second and subendocardial with T-wave inversion or S-T segment depression or both, persisting for ≥24 hours without loss of R-wave voltage or development of new Q waves. The location of acute MI was determined in all patients using standard ECG criteria[25] and chest pain was categorized by the standards of the New York Heart Association.[26]

Patients were added to the study over a 3-year period. Patients were excluded if imaging was unavailable or if they presented to the coronary care unit more than 48 hours after the event or had evidence of heart failure including symptoms of shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, ventricular gallop, or radiographic pulmonary blood flow redistribution. Similarly, patients presenting with shock or other conditions which required aggressive medical or surgical therapy and prevented patient participation or which made them intolerant to the multiple imaging procedures were excluded. All studies which were not clinically indicated for patient evaluation were obtained after the administration of full verbal and written informed consent.

Scintigraphic studies: Scintigraphic studies were done as soon as possible after infarction in accordance with clinical and technical restraints. All studies were performed during the acute phase of hospitalization within 10 days of the event; 60 (86%) of 70 scintigraphic studies were performed within the first 4 days of symptom onset. The latter included 22 of 25 MI scintigrams, 20 of 22 perfusion scintigrams, and 18 of 23 blood pool scintigrams.

Owing to clinical and technical restraints, 3 of the 25 patients did not have perfusion imaging, and 2 patients did not have blood pool scintigraphy.

All scintigraphic studies were performed on a Series 120 portable (Ohio Nuclear Corporation, Solon, Ohio; now a Division of Technicare) or a Pho Gamma V stationary scintillation camera (Searle Radiographics, Des Plaines, Illinois; now a Division of Siemens). Both perfusion scintigraphy using thallium-201 and MI scintigraphy using TcPYP were performed in 30° right anterior oblique, anterior 45° left anterior oblique, 60° left anterior oblique, and left lateral projections. Perfusion scintigraphy was performed 10 minutes after the intravenous injection of 1.5 to 2 mCi of thallium-201 employing a high-sensitivity collimator. The projection of the initial perfusion scintigram was acquired to 300,000 counts with each subsequent projection obtained to isotime. Infarct scintigrams were acquired according to a similar methodology 2 to 4 hours after the intravenous administration of 15 to 20 mCi of TcPYP using a low energy all-purpose collimator. Equilibrium blood pool scintigrams were initially performed using technetium-99m albumin in a dual-gated mode to a total of 400,000 counts in 40 ms end-diastolic and end-systolic frames acquired in 30° right anterior oblique and 60° left anterior oblique projections. In the most recent 18 patients, blood pool scintigraphy was performed with in vivo labeled red cells using standard multiple-gated methodology and a 28-frame multiple-gated movie acquired to a total of 4.5 million counts in both a 30° right anterior oblique and the "best septal" left anterior oblique projection; the latter best separated the right and left ventricles. While perfusion and infarct scintigrams were analyzed from analog polaroid images, initial blood pool studies were evaluated for the ejection fraction calculated from the geometric biplane method.[27] Later studies were acquired on a PDP 1140 (Digital Equipment, Maynard, Massachusetts) computer where counts ejection fraction was calculated according to standard methodologic methods from the best septal left anterior oblique image projected on a 128 × 128 matrix on a high quality Conrac (DeAnza, Burlingame, California) display.

The largest projected abnormality on both infarct and perfusion scintigrams was planimetered by 2 observers without knowledge of the clinical course and expressed in square centimeters using the field of view to calibrate the abnormality. The 2 observers agreed within 5% in their measured evaluation in 85% of cases. In the remainder, the area of abnormality was decided by agreement between the 2 observers. Perfusion abnormalities were also expressed as a percentage of the projected left ventricular area. Figure 1 demonstrates MI and perfusion scintigrams and their quantitation in a patient with a large lateral scintigraphic MI.

Clinical course and follow-up: All 25 patients survived the initial hospitalization and were followed for an average of 14 months (standard deviation 8 months, range 2 to 34). Two patients underwent coronary artery bypass graft surgery 2 and 14 months after their acute MI and were considered to end their follow-up period at the time of surgery. Patients were followed periodically at the University of California, San Francisco Cardiac Clinic, or by means of personal discussion with their outside physician and next of kin. Deaths were noted as cardiac if so recorded by the patient's physician or if occurring suddenly in the absence of symptoms or within

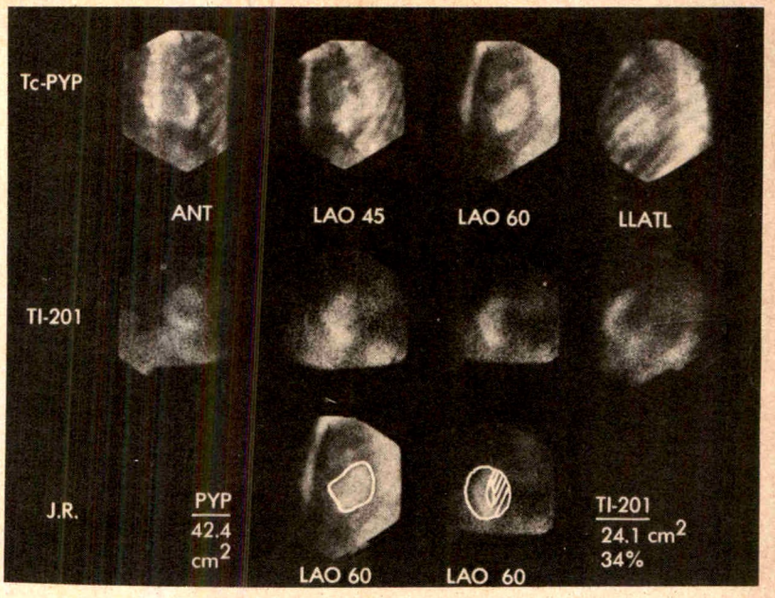

FIGURE 1. Scintigraphic sizing of acute myocardial infarction. Shown in the **upper panel** are TcPYP scintigrams and in the **center panel** thallium-201 (TI) myocardial perfusion scintigrams performed in anterior (ANT), 45° and 60° left anterior oblique (LAO), and left lateral (LLATL) projections in a patient with a large acute anterolateral myocardial infarction. In the **bottom panel,** the abnormal TcPYP area is outlined and expressed in cm^2. The perfusion image abnormality is similarly identified and expressed as an absolute abnormality and as a percentage of the projected left ventricular myocardium. J.R. = Patient 10 (see Table I).

6 hours of their appearance in the absence of another cause.

According to the long-term clinical course, determined by the follow-up protocol, patients were classified into 3 groups: (1) the asymptomatic group, composed of patients who, after hospital discharge, had no symptoms requiring treatment; (2) the symptomatic group, composed of patients who, at any time after hospital discharge, had anginal chest pain that required treatment or who had symptoms or signs of congestive heart failure as described above and which required treatment; (3) the deceased group, composed of patients who died of cardiac causes during the follow-up period. Both patients who underwent coronary artery bypass graft surgery had angina on follow-up, 1 in association with congestive heart failure.

Data analysis: To assess the prognostic value of scintigraphic indicators obtained early during initial hospitalization for acute MI, with respect to the long-term clinical course of patients after discharge, quantitative scintigraphic data from TcPYP infarct scintigrams, thallium-201 perfusion scintigrams, and blood pool scintigrams were consolidated according to the clinical group. Means and standard deviations of measurements of MI size, perfusion abnormalities, and left ventricular EF were calculated for the group of patients who died, for all patients who were alive at the time of last follow-up and who were symptomatic with angina or heart failure, and for all patients who were alive at the time of last follow-up and entirely asymptomatic. Quantitative differences in the size of scintigraphic abnormalities and ejection fractions were analyzed by means of a 1-way, nonweighted means analysis of variance. The between-groups variations were partitioned using planned or orthogonal comparisons: asymptomatic versus deceased, asymptomatic versus symptomatic, and symptomatic versus deceased. In addition, to compare all possible pairs of groups, a Student-Newman-Kuhles test was carried out. The scintigraphic indicators thus identified to be significantly different between groups were further analyzed by establishing absolute "break point" values which could be used to prospectively classify patients in those groups. For the deceased group, these break point levels were selected by determining the values of each scintigraphic indicator which yielded optimal detection of patients who died. With break point levels determined in this manner, each indicator was tested for accuracy of prediction of death or survival and development or absence of symptoms. Positive and negative predictive values were calculated as the number of patients with a given range of scintigraphic abnormality who were correctly classified divided by the total number of patients with this range of scintigraphic abnormality. Finally, the predictive accuracy of scintigraphic indicators was compared with that of clinical and historical variables.

Results

Among the 25 patients studied, 14 had an inferior MI and 11 an anterior MI. The MI was transmural in 22 and nontransmural in 3. There were 7 patients with a prior MI. The clinical findings on late follow-up in our 25 patients are detailed in Table I. On follow-up, 8 patients remained entirely asymptomatic, while 9 patients had symptoms, 2 patients had angina alone, 3 had congestive heart failure alone, and 4 had angina and congestive heart failure in the follow-up period. Among those in whom congestive failure developed, 2 patients were known to have another MI. Among those who died, 2 patients had sudden death and 4 had renewed chest pain, 1 of these with another MI and 3 with worsening heart failure. There was no significant relation between age, sex, site of MI, transmural nature of MI, the presence of prior MI, or the peak level of serum creatine kinase and the subsequent clinical findings on late follow-up. Both in our overall population of 62 patients[14] and among the 25 patients studied here, there was no relation between the size of scintigraphic abnormality and the time of imaging after the onset of symptoms.

Sixteen patients had rhythm disturbances; 5, conduction disturbances; and 4, combined rhythm and conduction abnormalities. Table II enumerates the individual rhythm and conduction abnormalities noted during the short-term hospitalization for acute MI and relates these to the late prognosis. Ventricular arrhythmias were not associated preferentially with any of the follow-up groups. However, both atrial arrhythmias and bifascicular block occurred in patients who later died or had symptoms, while heart block, requiring pacemaker insertion, appeared to be associated with a

TABLE I Patient Population and Test Results: Characteristics, Scintigraphic Findings, and Follow-Up Data on the 25 Patients Studied

Patient	Age (yr) & Sex	Type of Infarct	Prior MI	Follow-Up (mo)	Tl-201 (cm^2)	Tl-201 (%)	TcPYP (cm^2)	EF (%)	Peak CK	Peak MB
Asymptomatic at Last Follow-Up										
1	64M	TM, ANT	No	34	16	20	23	43	2,480	347
2	47M	TM, INF	No	12	10	15	16	45	1,688	304
3	53M	TM, INF	No	20	9	13	NEG	85	422	36
4	81M	TM, ANT, SEPT	Yes	5	8	11	4	47	286	26
5	57M	TM, INF	No	13	25	35	21	45	950	248
6	37M	TM, ANT	No	14	19	31	18	52	1,724	328
7	45M	TM, INF	Yes	32	11	16	8	45	960	269
8	48M	TM, INF	No	8	13	22	17	. . .	907	92
Had Angina and No CHF										
9	75M	SE, INF	Yes	21	14	21	NEG	48	74	14
10	50M	TM, INF, LAT	No	12	24	34	42	44	1,470	250
Had CHF and No Angina										
11	78F	TM, ANT	No	20	36	38	22	45	1,756	509
12	76F	TM, INF	No	5	11	19	19	58	475	33
13	44M	TM, ANT	Yes	14	41	55	60	37	. . .	. . .
Had CHF and Angina										
14	46M	TM, INF	Yes	23	. . .	. . .	34	20	1,662	620
15	69M	SE, ANT	No	14	43	50	49	40	221	25
16	41M	TM, INF	No	33	18	30	9	41	1,108	188
17	72F	TM, ANT	No	34	20	33	42	41	1,020	224
Died										
18	67F	TM, INF	No	20	38	40	27	38	2,288	824
19	61M	TM, INF	No	10	. . .	. . .	NEG	. . .	351	53
20	88M	TM, INF	No	5	. . .	. . .	20	50	349	10
21	67M	SE, ANT	No	5	22	45	66	48	1,080	410
22	67M	TM, ANT, SEPT	No	6	33	44	47	58	1,116	379
23	60M	TM, INF	Yes	2	17	40	42	51	1,022	123
24	70M	TM, ANT, LAT	Yes	2	61	54	48	32	430	58
25	73F	TM, ANT, LAT	No	15	20	31	37	35	908	200

CHF = congestive heart failure; CK = creatine kinase; EF = ejection fraction; INF = inferior; LAT = lateral; SE = subendocardial; SEPT = septal; TM = transmural; Tl-201 = thallium-201.

more benign clinical course in this late follow-up study.

Patients in the deceased group had significantly larger TcPYP abnormalities (36 ± 20 cm^2), absolute perfusion abnormalities (32 ± 16 cm^2), and percent left ventricular involvement (42 ± 8%) on perfusion scintigraphy than the asymptomatic group (13 ± 8 cm^2, 14 ± 6 cm^2, and 20 ± 9%; $p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively). While the absolute abnormality on TcPYP scintigraphy and perfusion scintigraphy was larger in the symptomatic group than in the asymptomatic group, it was not significantly different. In the symptomatic group only the percent left ventricular involvement on perfusion scintigraphy (35 ± 13%) was significantly larger than in the asymptomatic group (20 ± 9%, $p > 0.01$). The left ventricular EF was not significantly different between groups and could not differentiate asymptomatic survivors from symptomatic survivors or those who died. Perfusion scintigraphic abnormalities expressed as a percentage of left ven-

TABLE II Rhythm and Conduction Abnormalities: Relation Between Rhythm and Conduction Disturbances and Late Clinical Course

Late Clinical Course	Rhythm Abnormalities				Conduction Abnormalities	
	Ventricular Arrhythmias					
	VF	VT	Complex PVC	Atrial Arrhythmias: AF/AFL	Heart Block	Bifascicular Block
Asymptomatic (n = 8)	3	2	1	0	4	0
Symptomatic (n = 9)	1	2	2	3 (1)	0	2
Died (n = 8)	2	0	2	5 (2)	1	2
Total (n = 25)	6	4	5	8 (3)	5	4

Parentheses indicate patients with both atrial and ventricular arrhythmias.
AF = atrial fibrillation; AFL = atrial flutter; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

tricular involvement were significantly larger both in the deceased group (42 ± 8%, p <0.01) and the symptomatic group (35 ± 13%, p <0.01) than in the asymptomatic group (20 ± 9%). Enzyme levels failed to differentiate the groups. These findings are summarized in Figure 2.

Breakpoint values of 20 cm^2 for the absolute perfusion abnormality and 33% for the perfusion abnormality expressed as a percentage of left ventricular involvement succeeded in identifying 7 of 8 asymptomatic survivors who had absolute perfusion abnormalities <20 cm^2 or 33%. These values also succeeded in identifying 5 of 8 symptomatic survivors and 5 of 6 patients among those who died who had absolute perfusion abnormalities >20 cm^2 or which projected as >33% of the left ventricular area. Similarly, a breakpoint value of 25 cm^2 for the absolute size of the TcPYP infarct abnormality identified all 8 asymptomatic survivors, each of whom had scintigraphic infarct size <25 cm^2, and also identified 5 of 9 symptomatic survivors and 6 of 8 patients who died with scintigraphic infarct size >25 cm^2.

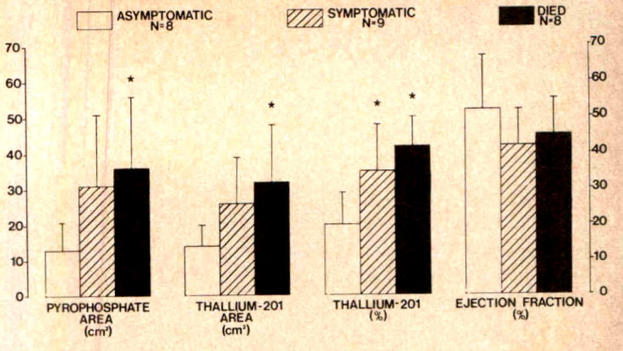

FIGURE 2. Scintigraphic parameters of acute infarction related to late prognosis. The percent perfusion abnormality appeared to best separate asymptomatic survivors from symptomatic survivors and those who died. See text for explanation of **asterisks.**

Discussion

Acute MI size has been shown to be related to the clinical outcome after the event.[2] A reliable noninvasive method for estimating acute MI size can have significant prognostic impact in patients. Initial studies would indicate that scintigraphic variables offer a relatively convenient, noninvasive marker for myocardial infarction size[9,10,28,29] and are shown in this study to allow identification of important clinical subgroups.

Advanced arrhythmias and conduction abnormalities occur frequently after MI and often appear to be related to severe abnormalities of ventricular function and a generally reduced prognosis.[19,22] The current investigation employed scintigraphic studies to separate, for the first time, poor and good prognosis subgroups from the overall population presenting with rhythm and conduction disturbances in the setting of acute MI and well-preserved left ventricular function.

Despite the small patient population, acute scintigraphic indicators of MI size and relative myocardial perfusion were able, unlike other variables, to discriminate quite well between patients who survived with a benign asymptomatic course and those who died. Although atrial fibrillation is related to a poor prognosis after acute MI,[30] this relation may well be indirect. Here, atrial arrhythmias were associated with larger scintigraphic abnormalities, and MI size may be the important prognostic factor. It is likely that part of the particularly high prognostic value of the large scintigraphic abnormality provides some measure of reserve capability and relates to an expression of patient vulnerability. This parallels the work of Sharpe et al,[31] who found an inverse relation between left ventricular stroke work index and scintigraphic measured TcPYP MI size.

Since early perfusion scintigraphy and not infarct scintigraphy could best differentiate among the subgroups during the late clinical course, the prognosis of these patients is likely related not only to the size of acute infarction but also to the extent of MI-related myocardial ischemia. The ability of the scintigraphic measure of perfusion to separate prognostic subgroups supports data relating to the size of the perfusion scintigraphic defect to prognosis late after acute MI in patients presenting acutely in Killip classes 1 or 2.[13] These authors also believe that acute variables of myocardial perfusion yield the most discriminatory indexes for late prognosis since such prognosis is likely related not only to the absolute amount of infarcted myocardium but also to the quantity of related ischemic myocardium at risk. The perfusion scintigram, alone among these studies evaluated, provides such a visual assessment.[32]

Left ventricular EF may vary considerably in patients after infarction regardless of the apparent clinical level of ventricular function.[14,31,33] Scintigraphic EF has been shown to have prognostic value in studies conducted in unselected populations of patients with acute MI.[33] Here, however, the range of EF was relatively narrow and left ventricular EF measured early after the event was of little value for prognostic purposes in this select group of patients presenting without evidence of congestive heart failure. Prior assessment of percent abnormally contracting segment applied in the parent population of 62 patients showed no superior prognostic value to that of the more easily acquired counts EF.[14]

Patients who have rhythm and conduction disturbances without congestive heart failure during acute MI may follow an uncomplicated or a complicated late clinical course. This study demonstrates for the first time that early scintigraphic measurements of MI and abnormal perfusion, but not left ventricular EF, correlate with the late clinical course. This would imply that the late clinical course in these patients can be identified early after infarction from scintigraphic variables. Control of rhythm and conduction disturbances during the acute phase of MI, accomplished in all patients studied here, does not necessarily presage a good prognosis. Prognosis seems more related to the extent of acute myocardial damage, reversible or irreversible, and the extent of such damage can best be measured scintigraphically. An anterior site, transmural distribution, and occurrence of prior MI tended to relate to larger scintigraphic defects and a poor prognosis in

the larger population of 62 patients.[14] A lack of correlation between scintigraphic and enzymatic parameters may be due in part to the fact that scintigraphic defects, as evaluated herein, are area measurements, related in some cases to the extent of ischemia as well as infarction, while enzymes measure infarct density and vary with unpredictable kinetic factors.[8,29]

The size of perfusion scintigraphic abnormalities need not relate absolutely to the extent of pathologic damage and in previous studies using similar methods, such scintigraphic measures have overestimated the pathologic MI size.[10] Yet, the size of the perfusion defect was quite discriminating for prognosis when expressed as a percentage of the overall projected left ventricular myocardium. This runs parallel to pathologic studies relating the extent of myocardial necrosis to prognosis after MI,[3] and the scintigraphic percentage related to a poor prognosis appears to be in the range of 30 to 35% of left ventricular involvement on the perfusion scintigram, similar to the 40% rate quoted on pathologic study. Like the findings of others,[15,33] resting left ventricular function was of limited prognostic value in this study, largely owing to the subgroup of patients evaluated in which there were only 5 patients with a left ventricular EF <40%. While each of these 5 had congestive heart failure or died, 10 other patients with a higher EF also shared a common prognosis. However, not a single patient, asymptomatic on follow-up, had a left ventricular EF <40%. This lack of prognostic sensitivity in the presence of prognostic specificity is likely related to the fact that, while the perfusion scintigram provides a measure of both regions of ischemia and infarction, left ventricular functional assessment reflects the sum of the global functional decrement owing to these 2 variables, but modified in an unpredictable way by the state of the unaffected ventricle and the premorbid level of ventricular function. Recent work indicates the improved prognostic value of left ventricular functional variables measured on stress blood pool scintigraphy in the post-MI period.[34]

Quantitation was carried out by a manual method necessitated by the tools available at the institution of study. However, reproducibility was excellent for infarct and perfusion images. Intraobserver variations (mean ± standard deviation) were ±4% and ±6%, while interobserver variability measured ±6% and ±7%, respectively. Although new computer methods might further objectify results and add significance to our findings, other groups have shown close agreement between manual quantitative methods and objective computer methods.[10,11,13] Regardless of the method of quantitation employed, the assessment of planar scintigraphic images will always find difficulty in the case of inferior and nontransmural MI.[35]

We sought to assess the extent of MI, related perfusion, and functional abnormalities in the immediate post-MI period. This cannot always be done owing to clinical and technical factors. It has been documented that scintigraphic values, and particularly perfusion scintigraphic abnormalities, appear to improve when studied serially in many patients following acute MI.[36] Nonetheless, in the present study, scintigraphic studies, and particularly perfusion scintigraphic studies, were able to discriminate among prognostic subgroups in spite of the fact that rare studies were obtained as late as 10 days after the event. There was no significant difference in the scintigraphic defect size or related prognostic value of the scintigraphic study among these patients studied at varying intervals after symptom onset. This and previous studies suggest that the measurement of scintigraphic defect size, days after infarction, can have significant prognostic value. While quite reproducible, image measurements made here lack the full objectivity and reliability of computer methods. Nevertheless, this assessment of analog images proved valuable for the assessment of prognosis. While computer methods might enhance such objective, quantitative data and possibly add to its prognostic value, the prognostic information is apparently already present on analog images. Similarly, owing to technical advances, left ventricular EF was measured by 2 different methods during the course of this evaluation. Both methods have been shown highly accurate and reproducible by us[37,38] and others.[39] Further studies, applying yet more quantitative methods, could add prognostic value to the scintigraphic results, rendering them of further specific use. The data presented here suggest that a scintigraphic assessment of the acute infarct patient, specifically presenting with rhythm and conduction disturbances but in the absence of heart failure, could provide an accurate statistical probability of late patient prognosis. In many cases, such prognostic data could be extremely important in the consideration and implementation of patient management in the acute infarct setting and thereafter.

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Differentiation Between Right and Circumflex Coronary Artery Disease on Thallium Myocardial Perfusion Scanning

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Thallium defects in the inferior and lateral walls of the heart were correlated with right and circumflex coronary artery disease (CAD) in 405 patients who underwent coronary arteriography. In the 102 patients with either single right or left circumflex (LC) CAD, inferior segment defects (anterior view) were associated with right CAD, and both lateral segment defects (40° left anterior oblique view) and posteroinferior defects (60° left anterior oblique view) were associated with LC CAD. In all 405 patients, inferior segment defects had a sensitivity of 65%, a specificity of 92%, and a predictive accuracy of 89% for right CAD, and lateral segment defects had a sensitivity of 52%, a specificity of 96%, and a predictive accuracy of 90% for LC CAD. Posteroinferior defects had a low predictive accuracy for narrowing in either artery. The presence or absence of concomitant anterior defects did not alter these results. Narrowing in both right and LC coronary arteries was best identified by a combination of inferior and lateral segment defects (sensitivity 30%, specificity 96%, predictive accuracy 72%). Narrowing in only 1 of these 2 arteries was best identified by a combination of inferior segment without lateral segment defects for right CAD (sensitivity 63%, specificity 86%, predictive accuracy 55%) and lateral segment without inferior segment defects for LC CAD (sensitivity 45%, specificity 92%, predictive accuracy 57%). Thallium scanning identifies significant narrowing in the right and LC coronary arteries, and these may be separated by the pattern of defects.

Thallium-201 myocardial perfusion scanning may help both to diagnose coronary artery disease (CAD) and to localize the area of ischemia.[1–10] Thallium perfusion defects in the anterior wall of the heart strongly suggest significant narrowing of the left anterior descending coronary artery,[6–10] but defects in the inferior and lateral walls may result from obstruction in either the right or the left circumflex (LC) coronary artery.[8,10] This study examines the distribution of thallium defects within the inferior and lateral walls to predict whether the right or the LC coronary artery was obstructed.

Methods

The study group included 405 consecutive patients (364 men and 41 women) who underwent exercise thallium scanning and coronary arteriography to assess CAD. Patients with a clinical diagnosis of valvular heart disease or cardiomyopathy and patients who had previous coronary bypass surgery were excluded. The mean age of the patients was 51 years (range 27 to 70). Exercise thallium scanning was performed within 6 months of coronary arteriography in all but 12 patients, in whom arteriography preceded thallium scanning by 6 to 24 months.

Exercise thallium-201 myocardial scanning: The patients performed maximal exercise on an upright bicycle ergometer or on a treadmill using a graded multistage, continuous protocol[3] until they experienced chest pain, breathlessness, or fatigue. A 12-lead electrocardiogram was recorded before and during each minute of exercise and recovery. At peak exercise, 1.5 to 2.0 mCi of thallium-201 was injected intravenously, and the patients exercised for another minute. Scanning was begun 5 minutes after the administration of thallium-201. Four views were obtained: anterior, 40° left anterior oblique, 60° left anterior oblique, and left lateral, using a Searle PHO-Gamma mobile camera and low-energy all-purpose parallel-hole collimator, as previously described.[3]

The scans were interpreted at the time of study from the original Polaroid scintiphotographs without computer enhancement or background subtraction, by the consensus of 3 experienced observers, who had no knowledge of the patients. Each of the 4 views was diagrammatically divided into 3 segments, as shown in Figure 1, and analyzed for the presence or absence of a thallium defect. The interconsensus variability for this technique is 7%.[8]

Defects in the inferior and lateral walls (Fig. 1) were defined as defects in 1 or more of the following segments: inferior in the anterior view, lateral in the 40° left anterior

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TABLE I Relation of Defects in Inferior and Lateral Walls and Specific Coronary Artery Disease

Diseased Coronary Arteries	Patients (n)	Defects in Inferior and Lateral Walls	No Defects in Inferior and Lateral Walls
Single coronary artery			
Right	61	55	6
LC	41	39	2
LAD	95	3	92
Two coronary arteries			
Right + LC	40	37	3
Right + LAD	35	22	13
LC + LAD	32	16	16
Three coronary arteries			
Right + LC + LAD	67	55	12
Normal	34	5	29
Total	405	232	173

LAD = left anterior descending; LC = left circumflex; normal = coronary arteries normal or insignificant narrowing.

TABLE II Incidence of Thallium Defects in Patients With Single Right and Left Circumflex Coronary Narrowing

Thallium Segments	Patients (n) With Thallium Defects: Right (n = 61) n	Right %	LC (n = 41) n	LC %	p Value
Anterior view					
ANT LAT	0	0	4	10	NS
APEX	37	61	26	61	NS
INF	47	77	8	19	<0.001
40° LAO view					
SEPT	12	10	4	10	NS
APEX	46	70	24	56	NS
LAT	3	5	28	68	<0.001
60° LAO view					
ANT SEPT	2	3	7	17	NS
APEX	43	66	19	41	NS
POST INF	35	57	34	83	<0.005
Left lateral					
ANT	0	0	2	12	NS
APEX	23	36	11	27	NS
POST	42	69	29	71	NS

ANT = anterior; ANT LAT = anterolateral; ANT SEPT = anteroseptal; LAO = left anterior oblique; LAT = lateral segment; LC = left circumflex coronary artery; NS = not significant; POST = posterior; SEPT = septal.

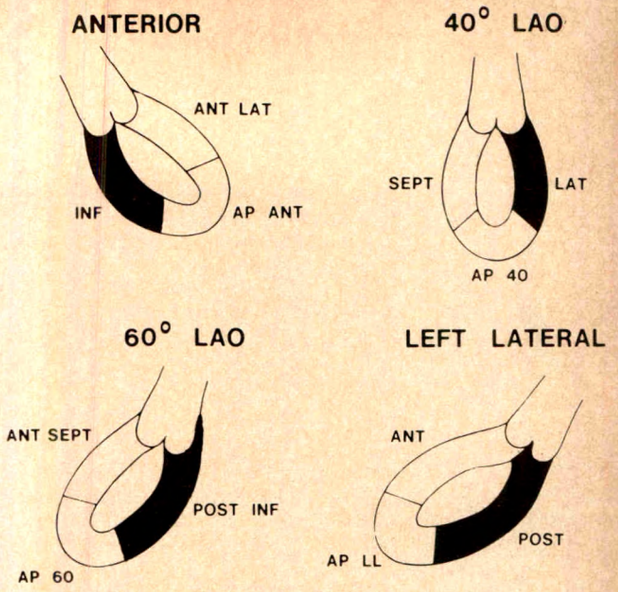

FIGURE 1. Location of inferior and lateral segments (**black**) in the 4 views of the thallium scan. ANT = anterior; ANT LAT = anterolateral; ANT SEPT = anteroseptal; AP ANT = apical, anterior view; AP LL = apical, left lateral view; AP 40 = apical, 40° LAO view; AP 60 = apical, 60° LAO view; INF = inferior segment; LAO = left anterior oblique; LAT = lateral; POST = posterior; POST INF = posteroinferior; SEPT = septal.

oblique view, posteroinferior in the 60° left anterior oblique view, and posterior in the left lateral view.[8] Anterior defects were defined as defects in 1 or more of the following segments: anterolateral in the anterior view, septal in the 40° left anterior oblique view, anteroseptal in the 60° left anterior oblique view, and anterior in the left lateral view.[8] Defects in the inferior, lateral, and anterior walls usually extended into the apical segments, which were defined as nonspecific.

Coronary arteriography: Selective coronary arteriography was performed in multiple projections using the Judkins or Sones techniques. Each study was reviewed by 2 experienced angiographers. The maximal luminal diameter narrowing for each major coronary artery was estimated visually, and mean measurements were used if the angiographers' opinions differed. Significant narrowing was defined as obstruction of at least 70% in the distribution of the left anterior descending, right, or LC coronary arteries or their major branches. All patients with left main coronary narrowing also had significant narrowing of the right coronary artery and were classified as 3-vessel disease.

Data analysis: Data were analyzed using the Yates-corrected chi-square test and the McNemar test.[11] Sensitivity was defined as the ratio of true positives to the sum of true positives and false negatives. Specificity was the ratio of true negatives to the sum of true negatives and false positives. Predictive accuracy of a positive test was the ratio of true positives to the sum of true positives and false positives.

Patients with single right and LC CAD were analyzed first to see which defect was most closely associated with narrowing in these 2 arteries. Then, all patients were analyzed to determine the predictive accuracy of defects in the inferior and lateral walls for narrowing of the right and LC coronary arteries.

Results

The distribution of CAD and the incidence of defects in the inferior and lateral walls in the 405 patients are shown in Table I.

Isolated right and left circumflex narrowing (Table II): In the 61 patients with isolated right CAD, thallium defects were most frequent in the inferior segment (77%), posterior segment (69%), and posteroinferior segment (57%). Apical defects also were frequent, whereas defects in the anterolateral, septal, anteroseptal, anterior, and lateral segments were uncommon. The typical pattern of thallium defects associated with isolated right CAD is shown in Figure 2.

When the 41 patients with isolated LC CAD were compared with patients with isolated right CAD, defects were more frequent in the lateral segment (68%, $p < 0.001$) and posteroinferior segment (83%, $p < 0.001$),

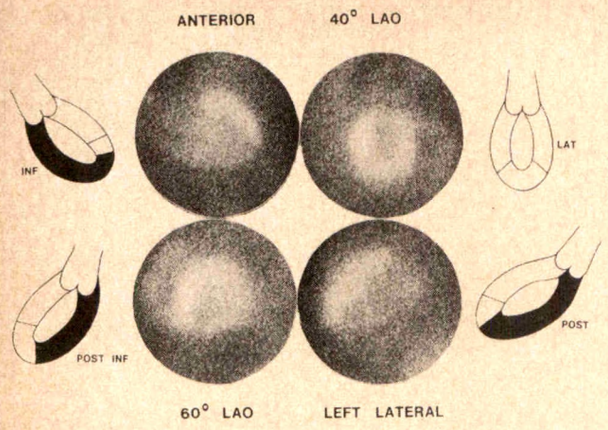

FIGURE 2. Exercise thallium scan of a patient with single-vessel right coronary artery disease. Perfusion defects are present in the inferior and apical segments in the anterior view, posteroinferior and apical segments in the 60° left anterior oblique view, and posterior and apical segments in the left lateral view, and are represented as **black areas** on the diagrams. Abbreviations as in Figure 1.

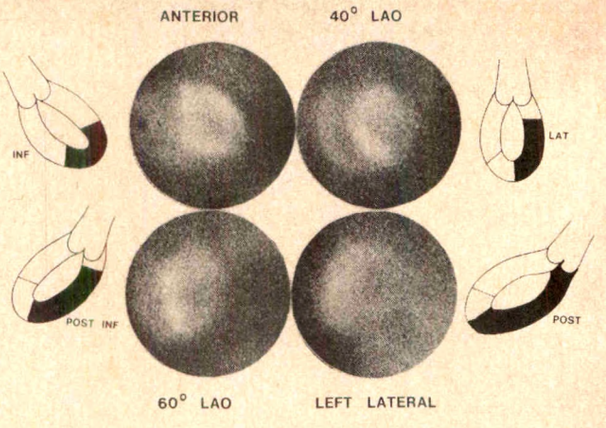

FIGURE 3. Exercise thallium scan of a patient with single-vessel left circumflex coronary artery disease. Perfusion defects are present in the apical segment in the anterior view, lateral and apical segments in the 40° left anterior oblique view, posteroinferior and apical segments in the 60° left anterior oblique view, and posterior segment in the left lateral view, and are represented as **black areas** on the diagrams. Abbreviations as in Figure 1.

and were less frequent in the inferior segment (19%, $p < 0.001$). The typical pattern of thallium defects in isolated LC CAD is shown in Figure 3. Because of the association of inferior defects with right CAD and lateral and posteroinferior defects with LC CAD, the sensitivity and specificity of these defects were examined in the total population.

Detection of right and circumflex disease (Tables III and IV): The sensitivity, specificity, and predictive accuracy of inferior, lateral, and posteroinferior defects for narrowing in right or LC coronary arteries were tested in all patients. Posteroinferior defects occurred equally in both right and LC CAD and were not analyzed further. Apical defects were not analyzed, as they can occur in patients with isolated left anterior descending, LC, and right CAD and have little localizing value.[5–9]

The relation between inferior thallium defects and right CAD is shown in Table III. Inferior defects had a sensitivity of 65% and a specificity of 92%. The predictive accuracy of inferior defects for right CAD was 89%, whereas in the absence of inferior defects there was still a 28% probability of right CAD (that is a predictive accuracy for absence of right CAD of 72%).

The relations between the lateral and posteroinferior defects and LC CAD are shown in Tables IV and V. The sensitivity of lateral defects for LC CAD was 52%, the specificity was 96%, and the predictive accuracy was 90%. Absence of lateral defects had a predictive accu-

TABLE III Sensitivity, Specificity, and Predictive Accuracy of Thallium Defect in Inferior Segment (INF) for Right Coronary Artery Disease (CAD)

		Right CAD (n = 203) +	Right CAD (n = 203) −	
INF Thallium Defect (n = 149)	+	132	17	Predictive Accuracy for Presence of Right CAD $= \frac{132}{149} = 89\%$
	−	71	185	Predictive Accuracy for Absence of Right CAD $= \frac{185}{256} = 72\%$

Sensitivity $= \frac{132}{203} = 65\%$ Specificity $= \frac{185}{202} = 92\%$

TABLE IV Sensitivity, Specificity, and Predictive Accuracy of Thallium Defect in Lateral Segment (LAT) for Left Circumflex (LC) Coronary Artery Disease (CAD)

		LC CAD (n = 180) +	LC CAD (n = 180) −	
LAT Thallium Defect (n = 103)	+	93	10	Predictive Accuracy for Presence of LC CAD $= \frac{93}{103} = 90\%$
	−	87	215	Predictive Accuracy for Absence of LC CAD $= \frac{215}{302} = 71\%$

Sensitivity $= \frac{93}{180} = 52\%$ Specificity $= \frac{215}{225} = 96\%$

TABLE V Sensitivity, Specificity, and Predictive Accuracy of Thallium Defect in Posteroinferior Segment (POST INF) for Left Circumflex (LC) Coronary Artery Disease (CAD)

		LC CAD (n = 180) +	LC CAD (n = 180) −	
POST INF Thallium Defect (n = 171)	+	123	48	Predictive Accuracy for Presence of LC CAD = 123/171 = 72%
	−	57	177	Predictive Accuracy for Absence of LC CAD = 177/234 = 76%

Sensitivity = 123/180 = 68% Specificity = 177/225 = 79%

racy for absence of LC CAD of 71%. The sensitivity of posteroinferior defects for LC CAD was 68%, the specificity was 79%, and the predictive accuracy was 72%. Absence of posteroinferior defects had a predictive accuracy for absence of LC CAD of 76%.

Influence of anterior defects: The predictive accuracies of inferior, lateral, and posteroinferior defects were compared in the 158 patients with and the 247 patients without anterior defects. The predictive accuracies of inferior defects for right CAD (93 versus 87%) and lateral defects for LC CAD disease (100 versus 87%) did not differ significantly in the presence and absence of anterior defects. Posteroinferior defects more accurately predicted LC CAD in patients with anterior defects than in patients without anterior defects (90 versus 66%; $p < 0.001$).

Right and left circumflex narrowing: The pattern of defects in patients with right and LC CAD is shown in Figure 4. Unlike in patients with isolated right and LC CAD, defects commonly occurred in both inferior and lateral segments. Various combinations of these and other segments were analyzed to determine whether disease in the right, LC, or both could be differentiated.

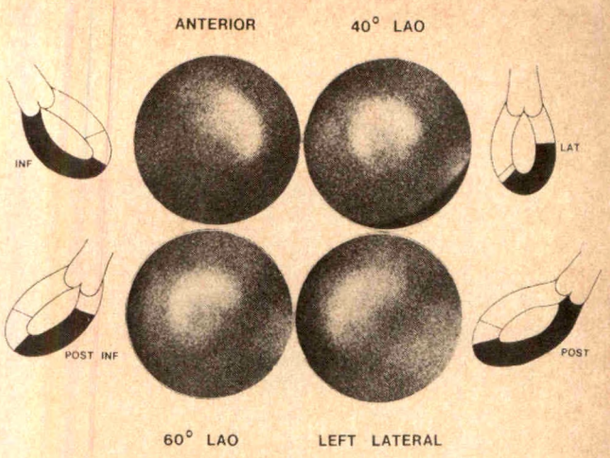

FIGURE 4. Exercise thallium scan of a patient with right and left circumflex coronary artery disease. Perfusion defects are present in the inferior segment in the anterior view, lateral segment in the 40° left anterior oblique view, posteroinferior segment in the 60° left anterior oblique view, posterior segment in the left lateral view, and in apical segments in all 4 views, and are represented as **black areas** on the diagrams. Abbreviations as in Figure 1.

The 3 combinations of defects in the inferior and lateral segments best differentiated CAD in the right, LC, and both (Table VI). Right CAD was best predicted by inferior defects without lateral defects (sensitivity 63%, specificity 86%, predictive accuracy 58%), but this combination also occurred in 32% of patients with both right and LC CAD. Left circumflex coronary artery disease was best predicted by lateral defects without inferior defects (sensitivity 45%, specificity 92%, predictive accuracy 57%), but this combination also occurred in 38% of patients with both right and LC CAD. Right and LC disease was best predicted by defects in both the inferior and lateral segments (sensitivity 30%, specificity 96%, predictive accuracy 72%).

Discussion

This study suggests that thallium defects in the inferior segment of the anterior view predict right CAD and defects in the lateral segment of the 40° left anterior oblique view predict LC CAD. Initially, we examined the pattern of thallium defects in single CAD, as in these patients the defects were related only to the diseased

TABLE VI Inferior and Lateral Thallium Defects in Patients With Disease in the Right, Left Circumflex, and Both Right and Left Circumflex Coronary Arteries

Segments With Thallium Defects*	Right CAD Only† (n = 96)		LC CAD Only† (n = 73)		Right + LC CAD† (n = 107)		Neither Right nor LC CAD (n = 8)	
	n	%	n	%	n	%	n	%
INF & not LAT (n = 104)	60	58	8	8	33	32	3	3
LAT & not INF (n = 58)	0	0	33	57	22	38	3	5
INF & LAT (n = 45)	7	16	6	13	32	72	0	0

* Irrespective of defects in other segments.
† Irrespective of disease in the left anterior descending coronary artery.
CAD = coronary artery disease; INF = inferior segment; LAT = lateral segment; LC = left circumflex.

single artery narrowed. Defects in the inferior segment were significantly more common in patients with right CAD and defects in the lateral and posteroinferior (60° left anterior oblique view) segments were significantly more common in patients with LC CAD. Previous studies have shown that inferior defects are common in right CAD, but too few patients with single-vessel LC CAD have been studied to determine the incidence of lateral segment defects.[6,8,9] In our study, there were 41 patients with single LC CAD; 28 (68%) had a perfusion defect in the lateral segment, whereas only 5% of patients with single right CAD had a similar defect.

After correlating scan defects in patients with single right CAD and LC CAD, defects in all 405 patients were analyzed and compared with the coronary anatomy. Inferior segment defects predicted right CAD (predictive accuracy 89%, specificity 92%). In contrast, lateral segment defects predicted LC CAD (predictive accuracy 90%, specificity 96%). Posteroinferior segment defects, although more common in LC CAD, occurred also in right CAD and did not predict either accurately.

Although defects in the inferior and lateral segments accurately predicted right and LC CAD, normal thallium uptake in these segments did not exclude narrowing of that artery. Approximately 30% of patients without inferior or lateral defects had significant narrowing of the right and LC coronary arteries. This poor predictive accuracy for the absence of significant narrowing is related to the low sensitivity of each of these segments for the presence of narrowing. Only 65% of patients with right CAD had inferior segment defects and only 52% of patients with LC CAD had lateral defects. These sensitivities are, however, similar to previous reports that have used visual interpretation of thallium scans.[6,7,10,12,13] Such interpretation does not detect narrowing in all significantly obstructed arteries.[6,7,12–14] As thallium defects represent relative abnormalities in myocardial perfusion, only the most ischemic vascular area will appear abnormal, and ischemia in another vascular territory may not be apparent. The vascular supply to a specific myocardial segment may vary in different patients, and overlap in an individual patient. Also, the severity of obstruction at angiography may be difficult to determine. Quantitative computer-assisted analysis improves interpretation.[13,14]

Perfusion defects in the inferior wall may be either underestimated or overestimated in the presence of anterior perfusion defects. Rigo et al[12] found that significant right and LC CAD may be missed if anterior defects are present, but there have been no previous studies to determine if inferior wall defects are overestimated in the presence of anterior defects. This study indicates that the predictive accuracies of inferior defects for right CAD and lateral defects for LC CAD did not significantly differ whether or not anterior defects were present. However, defects in the posteroinferior segment better predicted LC CAD when anterior defects were present and had a similar accuracy in defects in the lateral segment.

Previous studies have suggested that right CAD and LC CAD are difficult to separate on thallium scanning[8,10] because the vascular territories may vary. We found that inferior defects predicted right CAD and lateral defects predicted LC CAD; we analyzed combinations of defects to try to separate right from LC CAD. As expected, defects in the inferior without lateral defects were most common in right CAD but also occurred in 32% of patients with both right and LC CAD. Similarly, defects in the lateral without inferior defects were most common in LC CAD, but occurred in 38% of patients with CAD of both arteries. Defects in both the inferior and lateral segments occurred only occasionally in right and LC CAD and were suggestive of CAD in both.

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Left Ventricular End-Systolic Pressure-Volume Relation

A Combined Radionuclide and Hemodynamic Study

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This study examines the effect of increasing heart rate by atrial pacing on the left ventricular end-systolic pressure-volume relation and determines whether peak pressure can be used instead of end-systolic pressure. Measurements were made of cardiac output (by thermodilution), pulmonary arterial pressure, ejection fraction (by radionuclide angiography), and aortic pressure (by intraarterial catheter). End-systolic pressure was measured at the dicrotic notch. The end-diastolic and end-systolic volumes were determined from the ejection fraction and cardiac output. There was excellent correlation in pressure-volume relation determined by peak pressure and end-systolic pressure ($r = 0.95$). In 8 normal subjects there was <5% change in ejection fraction, a decrease in end-systolic volume, ≥30% increase in end-systolic pressure/end-systolic volume, and no change in pulmonary arterial pressure with pacing. Of 20 patients with coronary artery disease, 9 patients had ≥5% decrease in ejection fraction, 6 had an increase in end-systolic volume, and 14 had <30% increase in end-systolic pressure/end-systolic volume with pacing ($p < 0.05$). Thus (1) peak systolic pressure can be used reliably instead of end-systolic pressure; (2) atrial pacing has a positive inotropic effect in normal subjects—the minimal increase (30%) in end-systolic pressure/end-systolic volume is similar to the increase (35%) reported during exercise; (3) abnormal changes in end-systolic pressure/end-systolic volume in coronary artery disease are more common than changes in either ejection fraction or end-systolic volume with atrial pacing.

Several studies have used radionuclide ventriculography at rest and during exercise to evaluate left ventricular (LV) function.[1–3] Atrial pacing has also frequently been used to induce myocardial ischemia.[4–17] In experimental animals, the isolated left ventricle shows a linear end-systolic pressure-volume relation that is not dependent on the preload.[18] The slope of this relation is determined by the contractile state and is increased by positive inotropic interventions.[18,19] Recently, radionuclide studies have used the pressure-volume relations as a means of assessing LV function.[1] In these studies, peak pressure was used instead of end-systolic pressure, as was originally suggested.[18] This study examines the effects of increasing heart rate by atrial pacing on the end-systolic pressure-volume relation and determines whether peak pressure can be used instead of end-systolic pressure.

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Methods

The patient population consisted of 8 normal subjects and 20 patients with coronary artery disease (CAD). The normal subjects (6 men and 2 women; age range 37 to 67 years, mean 37) had normal coronary angiograms. The patients with CAD had stable angina pectoris and were found (by coronary arteriography) to have ≥70% diameter narrowing of 1 vessel (9 patients), 2 vessels (6 patients), or 3 vessels (5 patients). There were 17 men and 3 women, with an age range of 38 to 73 years (mean 55). Nitrates were withheld for at least 2 hours before the study but propranolol, which was prescribed for 12 patients, was not discontinued. There were no complications.

The pacing studies were performed with the patient in the supine position. Three catheters were inserted percutaneously with the patient under local anesthesia with lidocaine. First, a 6Fr Gorlin catheter or a 6Fr NBIH catheter was inserted by way of the left antecubital vein and positioned by means of fluoroscopy in the coronary sinus. This catheter was used for pacing. Second, a 7Fr triple-lumen balloon-tipped thermodilution catheter was inserted by way of a femoral vein and

TABLE I Hemodynamic Data at Rest and During Pacing

	Normal (n = 8)			CAD (n = 10): Group I			CAD (n = 10): Group II					
			p Value:			p Value:				p Value		
	C	P	C vs P	C	P	C vs P	C	P_1	P_2	C vs P_1	C vs P_2	P_1 vs P_2
HR	72 ± 8	123 ± 11	<0.001	74 ± 13	112 ± 17	<0.001	67 ± 9	99 ± 4	130 ± 10	<0.001	<0.001	<0.001
PA	16 ± 5	16 ± 6	NS	15 ± 3	15 ± 4	NS	19 ± 4	18 ± 5	23 ± 5	NS	<0.01	<0.02
AO	96 ± 7	101 ± 5	NS	97 ± 9	101 ± 11	NS	106 ± 8	114 ± 13	118 ± 12	<0.05	<0.01	NS
CI	3.2 ± 0.6	3.3 ± 0.6	NS	2.6 ± 0.4	2.7 ± 0.5	NS	2.9 ± 0.4	3.2 ± 0.6	3.0 ± 0.6	<0.02	NS	NS
EDVI	79 ± 13	47 ± 8	<0.001	81 ± 26	61 ± 23	<0.001	102 ± 26	76 ± 26	65 ± 26	<0.001	<0.001	NS
ESVI	35 ± 6	21 ± 5	<0.001	44 ± 23	36 ± 20	<0.05	58 ± 20	44 ± 21	42 ± 24	<0.001	<0.01	NS
EF	54 ± 3	56 ± 5	NS	48 ± 12	44 ± 10	NS	45 ± 7	45 ± 8	40 ± 12	NS	NS	NS
ESP/ESV	1.5 ± 0.4	2.6 ± 0.8	<0.001	1.6 ± 1.1	1.8 ± 0.9	NS	1.2 ± 0.6	1.7 ± 0.8	2.0 ± 1.4	<0.01	<0.02	NS

AO = mean aortic pressure (mm Hg); C = control; CAD = coronary artery disease; CI = cardiac index (liters/min/m^2); EDVI = end-diastolic volume index (ml/m^2); EF = left ventricular ejection fraction (%); ESP/ESV = end-systolic pressure/end-systolic volume; ESVI = end-systolic volume index (ml/m^2); NS = not significant; P = pacing; P_1 = submaximal pacing; P_2 = maximal pacing; PA = mean pulmonary artery pressure (mm Hg). EDVI and ESVI were derived from the thermodilution and radionuclide angiographic measurements according to Equations 2 and 3.

advanced into the pulmonary artery. This catheter was used to measure pulmonary artery pressure and cardiac output. Third, a short (6 inch) 6Fr Teflon® catheter was inserted into a femoral artery to monitor systemic pressure. After the catheters were in position, we obtained baseline measurements of the pulmonary artery and the aortic pressures. End-systolic pressure was measured at the level of the dicrotic notch.

Pacing was then begun with gradual increments of heart rate by 10 beats/min. Pacing was continued for a minimum of 2 minutes to assure hemodynamic stability, and then the measurements were repeated. In the first 10 patients with CAD (Group I), pacing was done at 1 rate. The endpoints of pacing in these patients were the development of Wenckebach atrioventricular block, or severe angina pectoris, or at least 2 mm S-T segment depression. In the last 10 patients, pacing studies were performed at 2 different rates (Group II). During the first study, the heart rate was increased by at least 20 beats/min above the control rate; during the second pacing study, the pacing rate was determined by 1 or more of the pacing endpoints described above.

Radionuclide angiograms were obtained in the control state and during pacing. All radionuclide angiography studies were performed in the anterior projection by the first-pass method with a computerized multicrystal camera (Baird-Atomic System-77).

Radionuclide angiograms were processed to measure LV ejection fraction, end-diastolic volume, and end-systolic volume using the computer software incorporated into the Baird-Atomic System.[20,21] The reliability and reproducibility of the method have been previously reported.[2,3,20] The LV end-diastolic volume and end-systolic volume were derived as follows by an independent method using the cardiac output determined by the thermodilution method, and the ejection fraction determined by the radionuclide angiogram: Stroke volume (milliliters by thermodilution) = cardiac output (milliliters/minute by thermodilution)/heart rate (beats/minute) (Equation 1). This stroke volume was then used in the next 2 equations: End-diastolic volume (milliliters) = stroke volume (milliliters)/ejection fraction (%) (Equation 2); and End-systolic volume (milliliters) = end-diastolic volume (milliliters) − stroke volume (milliliters) (Equation 3).

Statistical analysis: The results are expressed as mean ± standard deviation (SD) when appropriate. Differences between the rest and pacing studies were analyzed by the paired *t* test or analysis of variance. Comparison of volume measurements by different methods was performed by linear correlation analysis.

Results

Clinical, electrocardiographic, and hemodynamic changes during pacing: No normal subject had angina or S-T depression during pacing. In 11 patients (55%) with CAD, angina or S-T depression (or both) developed during pacing. The hemodynamic data in normal subjects and in patients with CAD at rest and during pacing are shown in Table I.

Changes in ventricular function and volumes during pacing: In normal subjects, there were significant decreases in end-diastolic and end-systolic volumes during pacing (Fig. 1 and 2), while the change in the ejection fraction was 0 to 4% (Fig. 3). In the 10 patients with CAD who had 1 pacing study (Group I), 2 patients had ≥5% decrease in ejection fraction with pacing while among the remaining 10 patients who had studies at 2 pacing rates (Group II), 8 patients showed ≥5% decrease in the ejection fraction at the final pacing rate compared

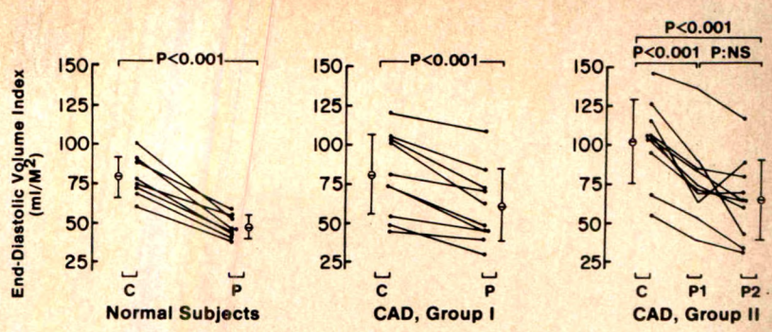

FIGURE 1. Changes in end-diastolic volume index during pacing in normal subjects and patients with coronary artery disease. C = control; CAD = coronary artery disease; P = pacing. Means ± standard deviations are shown.

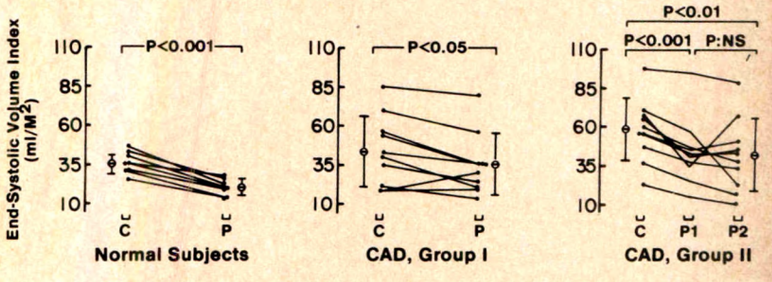

FIGURE 2. Changes in end-systolic volume index during pacing. C = control; CAD = coronary artery disease; P = pacing. Means ± standard deviations are shown.

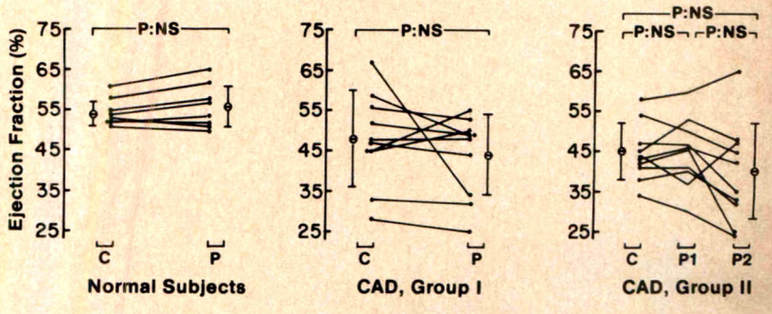

FIGURE 3. Changes in ejection fraction during pacing. C = control; CAD = coronary artery disease; P = pacing. Means ± standard deviations are shown.

with measurements at the first pacing rate (Fig. 3). The end-systolic volume increased during pacing in 2 patients in Group I and in 4 patients in Group II (Fig. 2). The end-diastolic volume decreased during pacing in both groups (Fig. 1). The end-systolic pressure-volume relation was determined in the normal subjects and in patients with CAD by using either peak systolic pressure or end-systolic pressure. The correlation between peak pressure-to-end-systolic volume ratio and the end-systolic pressure-to-end-systolic volume ratio was excellent ($r = 0.95$) (Fig. 4). The end-systolic pressure to end-systolic volume ratio increased by ≥30% in normal subjects. On the other hand, 6 patients with CAD in Group I and 8 patients in Group II had <30% increase (Fig. 5). An abnormal increase in the end-systolic pressure/end-systolic volume ratio was more common than an abnormal response to the ejection fraction or an increase in end-systolic volume during pacing (70% versus 50% versus 30%, respectively) ($p < 0.05$, change in end-systolic pressure to volume ratio compared with increase in end-systolic volume).

An abnormal response of the ejection fraction to pacing was found in 4 of 9 patients with 1-vessel disease and in 5 of 11 patients with multivessel disease (p = not significant [NS]). An abnormal change in end-systolic pressure-to-end-systolic volume ratio was found in 4 of 9 patients with 1-vessel disease and in 10 of 11 patients with multivessel disease ($p < 0.05$). In evaluating the results in relation to resting LV function, an abnormal ejection fraction response was noted in 3 of 6 patients with normal function and in 6 of 14 patients with abnormal function, and abnormal pressure-volume relation was noted in 4 of 6 patients with normal function and in 10 of 14 patients with abnormal function (p = NS).

An abnormal response in ejection fraction was noted in 3 of 8 patients not receiving propranolol therapy and in 6 of 12 patients receiving propranolol therapy (p = NS), and an abnormal change in pressure-volume relation was noted in 5 patients not receiving propranolol therapy and in 9 patients receiving such therapy (p = NS).

The mean normalized systolic ejection rate (ejection fraction/ejection time) decreased in the normal subjects (0.32 ± 0.03 control versus 0.26 ± 0.02 s^{-1} pacing, <0.001), but increased in patients with CAD (1.51

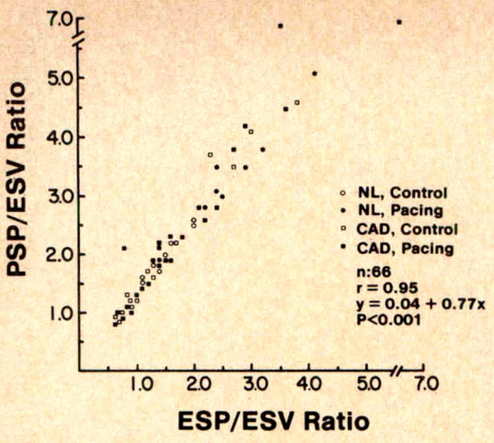

FIGURE 4. Correlation between the peak systolic pressure to end-systolic volume (PSP/ESV) ratio and the end-systolic pressure to end-systolic volume (ESP/ESV) ratio. CAD = patients with coronary artery disease.

0.38 control versus 1.69 ± 0.47 s^{-1} pacing, $p < 0.05$). All 8 normal subjects had a decrease while 14 of 20 patients with CAD had an increase ($p < 0.02$).

Finally, we found a good correlation between radionuclide derived end-diastolic and end-systolic LV volumes and similar volumes determined from thermodilution stroke volume and radionuclide ejection fraction (Equations 2 and 3) (Table II).

Discussion

We evaluated ventricular function by means of atrial pacing in normal subjects and in patients with CAD. We measured LV volumes by 2 methods: first, by radionuclide angiography, and second, by using the stroke volume derived from the thermodilution cardiac output and the ejection fraction derived from the radionuclide angiogram. This second method is not entirely independent from the first, but it is based on data derived by 2 reliable methods. This report, therefore, combines the best available methods for accurate measurement of ventricular volumes and has advantage over volume measurement by contrast angiography, since segmental wall-motion abnormalities during ischemia and changes in the shape of the ventricle may affect the reliability of geometric methods for volume measurements. In a

TABLE II Correlation Between Control and Pacing-Derived Volumes With Similar Measurements Obtained From Thermodilution Stroke Volume and Radionuclide Ejection Fraction

Normal subjects
EDV (using Equation 2) = 25 + 0.68 × EDV (by RNA), r = 0.80
ESV (using Equation 3) = 4.1 + 1.0 × ESV (by RNA), r = 0.86
Patients with coronary artery disease
EDV (using Equation 2) = 43 + 0.62 × EDV (by RNA), r = 0.80
ESV (using Equation 3) = 18 + 0.74 × ESV (by RNA), r = 0.85

EDV = end-diastolic volume (milliliters); ESV = end-systolic volume (milliliters); RNA = radionuclide angiography.

landmark study, Dwyer,[5] cognizant of this problem, obtained the ejection fraction from the end-diastolic volume measured by contrast angiography and the stroke volume measured by the dye dilution method. Ten patients with CAD were studied by pacing. Dwyer found that end-diastolic volume decreased in 9 patients and the ejection fraction decreased in 8 patients.

Other investigators have similarly shown a decrease in ejection fraction during pacing-induced ischemia.[6,15,16]

Our results showed that atrial pacing resulted in a significant decrease in end-diastolic volume in patients with CAD (Table I, Fig. 1). The decrease in end-diastolic volume was a continuous one, as demonstrated in 10 patients who had measurements at 2 pacing rates. In some patients there was a marked elevation in pulmonary artery pressure despite a decrease in end-diastolic volume during pacing-induced ischemia, indicating an alteration in LV compliance as reported by other investigators.[22,23]

Our results in normal subjects showed no significant change in the ejection fraction despite a decrease in end-diastolic volume during pacing (Fig. 1 and 3). The end-systolic pressure-to-end-systolic volume ratio increased in all. These results may suggest increased inotropicity with pacing, and therefore they support the findings of other investigators.[17,24–26] There was excellent correlation between peak systolic pressure-to-end-systolic volume ratio and the end-systolic pressure-to-end-systolic volume ratio (r = 0.95) (Fig. 4), thus indicating that the peak pressure can be used reliably instead of the end-systolic pressure. Although the dicrotic pressure and the end-systolic pressure are not identical, they are usually very similar.[27] We also found

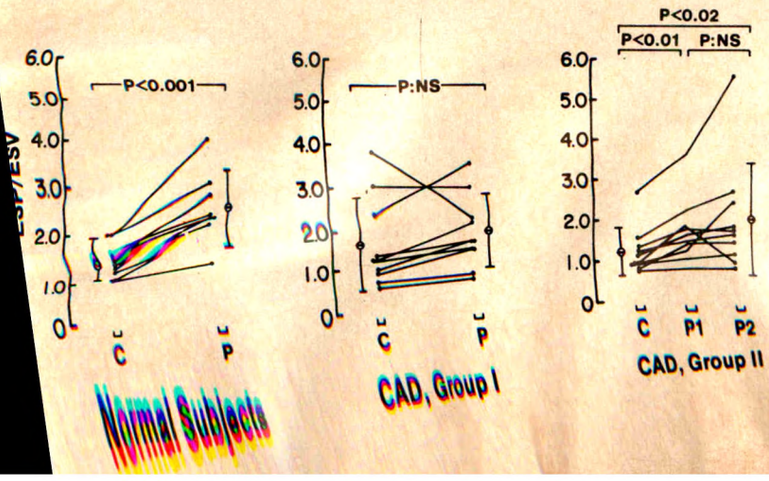

FIGURE 5. Changes in end-systolic pressure to end-systolic volume (ESP/ESV) ratio during pacing. C = control; CAD = coronary artery disease; P = pacing. Means ± standard deviations are shown.

that LV end-diastolic and end-systolic volumes can be reliably measured noninvasively by radionuclide angiography not only at rest but also during pacing-induced ischemia. These findings are important since the LV end-systolic pressure-volume relation can be determined by noninvasive measurements of the peak systemic pressure (by the cuff method) and the end-systolic volume (by radionuclide angiography). The minimal increase (30%) in the end-systolic pressure-to-end-systolic volume ratio in the normal subjects during pacing is similar to the minimal increase (35%) reported during exercise.[1]

Finally, an abnormal increase in end-systolic pressure-to-end-systolic volume ratio was seen in 14 patients (70%) with CAD, while only 6 patients (30%) had an increase in end-systolic volume ($p < 0.05$) and 10 patients (50%) had $\geq 5\%$ decrease in the ejection fraction with pacing. The normal subjects had a decrease in the mean normalized systolic ejection rate with pacing while patients with CAD had an increase. Since most patients had abnormal resting ejection fractions, the pacing studies were not done to diagnose CAD but rather to evaluate the pressure-volume changes.

Thus, peak pressure can be used reliably instead of end-systolic pressure; pacing has a positive inotropic effect in normal subjects; the minimal increase (30%) in end-systolic pressure-to-end-systolic volume ratio is similar to the increase (35%) reported during exercise; and abnormal changes in end-systolic pressure-volume relation are more frequent than changes in the ejection fraction or end-systolic volume during pacing.

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Comparison of Slow-Release Pindolol, Standard Pindolol, And Propranolol in Angina Pectoris

JOHN O. PARKER, MD

Twenty-two patients with chronic, stable, exercise-induced angina pectoris were assessed during periods of therapy with propranolol, standard-formulation pindolol, and a slow-release preparation of pindolol. Patients maintained diaries of the frequency of angina pectoris and nitroglycerin consumption and underwent treadmill exercise testing at 2 weekly intervals. No significant differences were observed in nitroglycerin consumption or anginal frequency during these 3 treatment programs. Resting heart rates were higher with pindolol than with propranolol, but no differences were noted between periods on standard and slow-release pindolol. Systolic and diastolic blood pressures were similar during therapy with these 3 treatment programs. Treadmill walking time to the development of moderate angina and systolic and diastolic blood pressure was similar during treatment with propranolol, standard-formulation pindolol, and slow-release pindolol. Exercise heart rates were slightly higher during therapy with slow-release pindolol than during standard-formulation pindolol. It is concluded that propranolol, pindolol, and slow-release pindolol are equally effective in the management of patients with chronic, stable, exercise-induced angina.

The beta adrenoreceptor blocking agent, pindolol, has been effective in the management of patients with stable exercise-induced angina pectoris.[1,2] Pindolol is a nonselective beta-blocking agent that possesses the strongest partial agonist activity of any of the currently available drugs with the property. Beta-blocking drugs with this intrinsic sympathomimetic activity (ISA) have potential advantages over agents lacking this property in that there is less depression of heart rate[2,3] and there may be protection against cardiac failure[4] and bronchial asthma.[5] The plasma half-life of pindolol is similar to that of propranolol, but the drug has been shown to be effective for longer periods.[6,7] Pindolol also differs from propranolol and most other beta-blocking drugs in that it undergoes less first-pass metabolism in the liver.[8]

A slow-release form of pindolol has been developed, and preliminary data obtained at rest and during exercise have shown this to have a prolonged duration of action.[9] These data suggest that the slow-release preparation would be effective in patients with angina pectoris when administered in a single daily dose.

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The present investigation was designed to compare the antianginal efficacy of slow-release pindolol given once daily with standard pindolol administered twice daily in patients with stable angina pectoris. The study also permitted a comparison between the effects of these 2 preparations of pindolol and standard propranolol administered 4 times daily.

Patients: Twenty-two male patients aged 44 to 70 years (mean 57.2) with chronic, stable angina pectoris participated in this investigation. The diagnosis of coronary artery disease was confirmed either by documentation of clinical and electrocardiographic evidence of previous myocardial infarction (7 patients) or demonstration of significant coronary artery disease by selective coronary angiography (21 patients). All patients gave an unequivocal history of exertional angina pectoris despite therapy, and all had positive exercise tests with angina during exercise and horizontal depression of the S-T segments of >1 mm for at least 80 ms after the J point. No patients had clinical evidence of abnormal left ventricular function or had previously been in heart failure.

All patients had been taking standard propranolol for at least 1 month before this investigation. Twenty-one patients were taking propranolol, 40 mg 4 times daily at 8 A.M., 1 P.M., 6 P.M., and midnight, and 1 patient, 40 mg twice daily at 8 A.M. and 8 P.M. All 22 patients were considered propranolol responders and 12 patients had

such improvement documented by treadmill exercise testing before and after initiation of therapy with propranolol. In these patients, exercise time to the development of moderate angina was prolonged by at least 60 seconds when examined 4 hours after a dose of propranolol. Nine of the 22 patients were taking oral nitrates, and these were continued throughout the investigation. Patients were taking nitroglycerin to treat episodes of chest pain, but none of the patients were using sublingual nitroglycerin in a prophylactic fashion. Informed, written consent was obtained from each subject.

Methods

Study design: Each patient had been on propranolol for at least 1 month and was familiar with treadmill exercise testing. Patients taking oral nitrate preparations continued on the same dose throughout this investigation. On the initial study day, patients were instructed to report to the laboratory after an overnight fast without taking their morning medications. Blood pressure and heart rate were recorded in the supine and upright postures, and a 12-lead electrocardiogram was obtained. At 8 A.M., the patients carried out a treadmill exercise test employing Bruce's protocol.[10] Patients were asked to indicate the time when angina pectoris first developed (P_1) and were encouraged to continue to exercise to the point where the angina pectoris became of moderate severity (P_2), at which time exercise was stopped. During the exercise period, modified lead V_5 was monitored and records were taken at 1-minute intervals during exercise and during a 5-minute recovery period for the determination of heart rate and the extent of S-T segment changes. Blood pressure was recorded by sphygmomanometry at the end of each 3-minute exercise stage, at P_1 and P_2, and at 1, 3, and 5 minutes of recovery. The time from the cessation of exercise to the disappearance of angina pectoris was also recorded.

After this study, the patients were randomized into 2 groups and entered a double blind cross-over study with standard pindolol and slow release pindolol employing the same total daily dose. The study design was as follows: *Group I (11 patients)*: study period (weeks 1 to 4): 8 A.M., slow release pindolol 20 mg plus pindolol placebo, and 8 P.M., pindolol placebo; study period (weeks 5 to 8): 8 A.M., standard pindolol 10 mg plus slow release pindolol placebo, and 8 P.M., standard pindolol 10 mg. *Group II (11 patients)*: These patients received active and placebo medications in the reverse order for the 2 study periods.

Patients were seen at 2 weekly intervals and were provided with a supply of medications and diaries to maintain a record of the frequency of anginal episodes and their nitroglycerin consumption. Patients came for assessment after 2, 4, 6, and 8 weeks on these treatment regimens. At these times, patients presented in the fasting stage without taking their morning medications and were asked not to smoke. Patients on oral nitrates did not take them on the morning of these studies and none of the patients took sublingual nitroglycerin within 2 hours of assessment.

Patients were assessed on each visit and their anginal diary and nitroglycerin consumption reviewed. The medication bottles were returned and a pill count done to assess compliance. Treadmill exercise test was carried out as just described.

After the 8-week period of these pindolol treatment regimes, the patients were returned to their previous therapy with propranolol. Patients continued to record anginal episodes and nitroglycerin consumption and after 2 weeks were assessed and underwent treadmill exercise testing.

Statistical analyses were performed by employing a Latin square design for comparisons of the 2 forms of pindolol. P values ≤ 0.05 are considered significant by this method. When comparisons were made between the propranolol and pindolol phases, the Bonferroni method for analysis of variance for repeated measurements was used.[11] P values ≤ 0.01 are considered significant with this method.

Results

All 22 patients completed this study. No significant side effects were reported when drug therapy was changed from propranolol to either formulation of pindolol or when the propranolol was reinstituted for the final 2 weeks of the study.

Resting hemodynamics (Table I): Values for heart rate and systolic and diastolic blood pressure in the supine and upright positions are shown for Groups I and II in Table I. Data are shown for the initial propranolol period, during therapy with standard and slow release pindolol, and during the final phase of therapy with propranolol. Heart rate was similar in the 2 groups during both periods on propranolol and was similar in the supine and upright postures. When patients were given pindolol, resting heart rate increased significantly in both the supine and upright postures ($p < 0.01$). No significant differences in heart rate were evident between the treatment periods and the 2 formulations of pindolol. Systolic and diastolic blood pressure was similar in both groups during each phase of the investigation with propranolol and with both forms of pindolol.

Frequency of angina pectoris (Table II): During the initial propranolol phase, patients in Group I and Group II experienced an average frequency of angina pectoris of 7.6 ± 1.8 (standard error of the mean) and 9.6 ± 3.3 episodes during a 2-week period. The difference between the 2 groups was not significant. There was a gradual decrease in the frequency of angina pectoris during the period of this investigation in both groups. These changes, which may have been due to a training effect, were not significant and the frequency of angina between the groups and within the groups was similar during both the propranolol and the pindolol phases of this study.

Nitroglycerin consumption (Table II): During the initial propranolol phase, patients in Group I and Group II consumed an average of 6.7 ± 3.2 and 8.5 ± 4.0 nitroglycerin tablets in a 2-week period. The difference between the 2 groups was not significant. As with the frequency of angina pectoris, there was a gradual reduction in nitroglycerin consumption over the period of this investigation. These changes were not significant, and thus, over the period of the study, nitroglycerin consumption between the groups and within the groups was similar during both the propranolol and the pindolol phases.

Exercise testing (Table II): Treadmill walking time to the onset of angina pectoris (P_1) was similar in Group I (4.8 ± 0.4 minutes) and Group II (3.9 ± 9.4 minutes) during the initial propranolol phase. The time to moderate angina (P_2) was also similar in the 2 groups: 7.0 ± 0.3 and 6.2 ± 0.4 minutes, respectively.

TABLE I Resting Hemodynamic Data

	Week 0	Week 4	Week 8	Week 10
	Group I (n = 11)			
	Prop	SR Pind	SF Pind	Prop
HR, supine (beats/min)	60 ± 3.2	68 ± 2.8*	68 ± 2.3*	61 ± 2.0
HR, upright (beats/min)	61 ± 2.9	76 ± 3.2*	72 ± 3.2*	64 ± 2.5
SBP, supine (mm Hg)	132 ± 3.7	131 ± 4.3	133 ± 4.9	130 ± 7.6
SBP, upright (mm Hg)	125 ± 5.5	120 ± 4.7	124 ± 5.7	123 ± 7.5
DBP, supine (mm Hg)	78 ± 1.8	77 ± 2.6	78 ± 2.3	78 ± 3.7
DBP, upright (mm Hg)	77 ± 2.3	74 ± 2.1	75 ± 3.2	74 ± 3.7
	Group II (n = 11)			
	Prop	SF Pind	SR Pind	Prop
HR, supine (beats/min)	58 ± 2.1	70 ± 2.6*	70 ± 3.5*	61 ± 2.5
HR, upright (beats/min)	63 ± 3.1	76 ± 3.3*	74 ± 3.1*	67 ± 2.6
SBP, supine (mm Hg)	135 ± 7.3	133 ± 5.6	132 ± 4.9	132 ± 6.2
SBP, upright (mm Hg)	132 ± 6.2	132 ± 5.8	128 ± 4.4	129 ± 6.0
DBP, supine (mm Hg)	76 ± 2.4	79 ± 2.6	78 ± 2.2	76 ± 2.9
DBP, upright (mm Hg)	77 ± 2.8	80 ± 2.8	79 ± 2.2	76 ± 3.2

* $p < 0.01$, comparison of values during pindolol and propranolol therapy by the Bonferroni method.
DBP = diastolic blood pressure; HR = heart rate; Prop = propranolol; SBP = systolic blood pressure; SF Pind = standard-formulation pindolol; SR Pind = slow-release pindolol.
Data shown are mean ± standard error.

When the patients in Group I were changed from propranolol to slow-release pindolol, treadmill walking time to P_1 was increased to 5.5 ± 0.4 minutes, a small but significant change ($p < 0.01$). Time to P_2 was also increased, being 8.0 ± 0.6 minutes, but this was not statistically significant. When these patients subsequently were changed to standard formulation pindolol, exercise time to P_1 and P_2 showed no further change and remained at approximately the same levels when the patients were changed back to propranolol for the final 2 weeks.

In Group II, the treadmill walking time to P_1 and P_2 showed no change from the initial propranolol phase to the phase with standard pindolol. When subsequently

TABLE II Clinical and Exercise Testing Data

	Week 0	Week 4	Week 8	Week 10
	Group I (n = 11)			
	Prop	SR Pind	SF Pind	Prop
AP	7.6 ± 1.8	7.2 ± 2.7	4.6 ± 1.4	3.3 ± 1.8
GTN	6.7 ± 3.2	5.4 ± 2.5	5.5 ± 2.6	4.9 ± 2.0
WT (P_1) (min)	4.8 ± 0.4	5.5 ± 0.4*	5.4 ± 0.3	5.0 ± 0.5
WT (P_2) (min)	7.0 ± 0.3	8.0 ± 0.6	7.6 ± 0.4	7.7 ± 0.5
(P_0) (min)	2.2 ± 0.4	2.1 ± 0.3	2.3 ± 0.4	2.6 ± 0.4
SBP (P_1) (mm Hg)	144 ± 5.4	136 ± 4.1	133 ± 5.2	141 ± 10.0
SBP (P_2) (mm Hg)	153 ± 6.5	137 ± 6.7	137 ± 6.0	151 ± 9.0
H-R (P_1) (beats/min)	104 ± 4.5	108 ± 5.2†	106 ± 3.4	103 ± 5.0
H-R (P_2) (beats/min)	114 ± 4.8	114 ± 3.6†	109 ± 3.4	113 ± 4.5
S-T (P_1) (mm)	−1.8 ± 0.3	−2.0 ± 0.3	−1.5 ± 0.3	−1.6 ± 0.5
S-T (P_2) (mm)	−2.6 ± 0.3	−2.5 ± 0.3	−1.9 ± 0.4	−2.2 ± 0.3
	Group II (n = 11)			
	Prop	SF Pind	SR Pind	Prop
AP	9.6 ± 3.3	7.3 ± 1.9	3.4 ± 1.0	7.7 ± 2.6
GTN	8.5 ± 4.0	4.2 ± 1.7	3.3 ± 1.7	5.2 ± 2.5
WT (P_1) (min)	3.9 ± 0.4	4.0 ± 0.3	4.9 ± 0.3†	4.1 ± 0.4
WT (P_2) (min)	6.2 ± 0.4	6.8 ± 0.3	6.6 ± 0.3	6.3 ± 0.3
(P_0) (min)	1.2 ± 0.3	1.9 ± 0.4	1.3 ± 0.2	1.8 ± 0.3
SBP (P_1) (mm Hg)	146 ± 4.2	141 ± 4.1	145 ± 4.4	137 ± 5.7
SBP (P_2) (mm Hg)	155 ± 4.7	146 ± 4.4	146 ± 5.3	147 ± 6.7
HR (P_1) (beats/min)	99 ± 3.2	101 ± 3.2	107 ± 3.4*,†	98 ± 3.4
HR (P_2) (beats/min)	107 ± 4.3	108 ± 4.2	110 ± 4.7†	100 ± 4.3
S-T (P_1) (mm)	−1.4 ± 0.3	−1.3 ± 0.3	−1.9 ± 0.4	−1.6 ± 0.2
S-T (P_2) (mm)	−2.2 ± 0.4	−2.2 ± 0.5	−2.6 ± 0.4	−2.5 ± 0.5

AP = angina pectoris during 2-week period; GTN = nitroglycerin consumption during 2-week period; HR = heart rate; P_1 = onset of angina pectoris; P_2 = development of moderate angina pectoris; P_0 = disappearance of angina during the recovery period; Prop = propranolol; SF Pind = standard-formulation pindolol; SR Pind = slow-release pindolol; S-T = S-T segment depression; WT = treadmill walking time.
* Statistical analysis by the Bonferroni method comparing periods on pindolol with propranolol ($p < 0.01$).
† Latin square design analysis, comparison of the 2 pindolol periods of study ($p < 0.05$).

placed on sustained release pindolol, the time to P_1 (4.9 ± 0.3 minutes) was significantly greater than that with standard pindolol (4.0 ± 0.3 min) ($p < 0.04$). However, no significant change was noted in time to P_2 during the various phases of the study in this group of patients. The time taken for angina to disappear after cessation of exercise was similar in all phases of the study.

The exercise heart rate during the 2 propranolol phases was similar. In both groups, the heart rates at the time of moderate angina during both slow release and standard formulation pindolol phases were similar to those during therapy with propranolol. Using Latin square design analyses during the 2 pindolol phases, there were small, but significant differences in heart rate at P_1 and P_2 with higher values of heart rate during the slow release phase than with the standard formulation phase.

Systolic and diastolic blood pressure was similar in Group I and Group II at both P_1 and P_2 during each phase of this investigation. S-T segments at rest and at P_1 and P_2 were similar in both groups at each phase of the study.

Discussion

Beta adrenoreceptor drugs are effective in the prophylactic management of patients with stable angina pectoris due to atherosclerotic heart disease. The therapeutic efficacy of this group of drugs is considered to be due to a decrease in left ventricular oxygen requirements secondary to reduced heart rate, systolic blood pressure, and myocardial contractility.[12] However, the slower heart rate and decreased contractility lead to increased left ventricular volume which tends to increase wall tension for any given blood pressure and may augment myocardial oxygen requirements.[13]

The beta adrenoreceptor drugs currently available for clinical use differ in some of their ancillary properties which may impact on their clinical usefulness. These properties include cardioselectivity, when agents block primarily $beta_1$ receptors, and the presence of ISA. Cardioselectivity is potentially advantageous when managing patients with reactive airway disease or patients with peripheral vascular disease in whom the absence of $beta_2$ blockade may lead to less bronchospasm and a smaller decline in muscle blood flow. Unfortunately, however, this cardioselectivity is most apparent at low concentrations, and with the doses commonly required to treat patients with angina pectoris and hypertension, cardioselectivity may be lost.[14]

The presence of ISA has potential benefits in patient management as beta-blocking drugs possessing this property have less effect on heart rate.[2,3] The presence of this partial agonist activity also may be important in maintenance of cardiac output both at rest and during exercise.[4] Thus, patients with resting bradycardia may be able to tolerate a beta-blocking drug with ISA better than a drug without this property.[4,5] It has also been suggested that patients with poor left ventricular function, obstructive airway disease, and peripheral vascular disease may tolerate this group of drugs better than drugs such as propranolol which do not have this property. There is also suggestive evidence that drugs possessing partial agonist activity may be associated with a lower incidence of fatigue than other beta-blocking drugs.[2]

Pindolol is a beta-blocking drug that is noncardioselective, but that has potent ISA, whereas propranolol, which is also noncardioselective, has no partial agonist activity. The present investigation was designed to compare the efficacy of a slow release form of pindolol with standard pindolol and to compare each of these formulations with standard propranolol. The comparison between the 2 types of pindolol was double-blind in nature and cross-over in design, whereas the propranolol phases of the investigation were open. Despite the limitations of the study design, the availability of objective data at rest and during exercise during the initial and final phases of the study while patients were receiving propranolol does provide useful comparative data regarding propranolol and the 2 formulations of pindolol.

This study did not attempt to assess the efficacy of these treatment programs on treadmill exercise tolerance throughout a 24-hour period. The timing of the exercise testing was such that each regimen was assessed at a time when the drug effects would be expected to be at a minimum. It is recognized that the clinical effects of both pindolol and propranolol are much longer in duration than would be suggested by their elimination half-lives. Thus, propranolol given twice daily has been as effective as 4 times daily therapy,[15] and treadmill exercise time to angina is prolonged for 8 to 12 hours after dosing.[16] In this study, the morning exercise test was carried out 8 hours after the last dose of propranolol, and exercise tolerance was similar to that seen 12 hours after standard formulation pindolol and 24 hours after slow-release pindolol.

Recordings of the frequency of angina pectoris and nitroglycerin consumption are of only limited value. In patients with stable angina pectoris, these variables vary directly with patient activities and in themselves are of little use in assessing clinical efficacy. Despite these reservations, this study showed similar anginal frequency and nitroglycerin consumption during the 2 pindolol phases, which in turn were similar to the periods of propranolol consumption. However, throughout the study period, there was a gradual diminution in the frequency of angina pectoris and also in nitroglycerin consumption, changes that are probably related to a training effect.

Hemodynamics at rest were similar during the 2 propranolol periods in both groups of patients. During pindolol therapy, the resting heart rates were significantly higher in both the slow release and the standard formulation phase of the investigation, reflecting the partial agonist activity of pindolol with resting heart rates increasing by approximately 10 beats/min over those levels recorded on propranolol. The resting heart rates were slightly higher after 4 weeks of therapy with slow-release pindolol than with standard formulation pindolol, but these differences were not statistically significant. Systolic and diastolic blood pressure was similar when patients were taking propranolol and both formulations of pindolol.

Exercise testing showed no major differences between propranolol and the 2 formulations of pindolol. Group I showed an increase in exercise time to the onset of angina when placed on slow-release pindolol. There was no change when subsequently given standard pindolol and propranolol and so this apparent improvement may be due to a training effect. However, there was no change in exercise time to the endpoint of moderate angina. Group II patients showed a small but significantly longer exercise time to the onset of angina while on slow-release pindolol than on standard pindolol. However, exercise times to the endpoint of moderate angina were similar while on these 3 regimens. While heart rates at rest were higher on pindolol than on propranolol, the exercise heart rate at the time of the development of moderate angina was similar during these treatment periods. Other investigators have suggested that during comparable levels of physical activity, the exercise heart rate is higher during pindolol therapy than during propranolol therapy.[2] The present study showed somewhat higher heart rates at the onset of angina when the patients were receiving slow-release pindolol than when receiving propranolol. However, no differences were seen when standard pindolol was given.

The partial agonist activity could have deleterious effects in patients with angina pectoris. The greater resting heart rate could lead to greater myocardial oxygen consumption, but the resting heart rate during pindolol therapy is usually similar to or less than that seen before initiation of therapy. The fact that the exercise heart rate was similar with pindolol and propranolol suggests that this property has little influence on heart rate during maximal exercise; other factors clearly are playing a major role in determining the heart rate response. Similarly, the presence of ISA may result in less depression of cardiac contractility and so blunt 1 of the beneficial influences of the adrenoreceptor agents. This may be the case at rest, but during exercise this factor appears to play only an insignificant role as exercise times were similar during therapy with propranolol and pindolol.

In many patients, symptomatic bradycardia develops with propranolol and similar beta-blocking drugs and may produce symptoms and be partly responsible for weakness, ease of fatigue, lassitude, and postural hypotension. These untoward effects may limit dosages so that therapeutic endpoints cannot be achieved. A drug possessing partial agonist activity is superior in this group of patients as the resting heart rate may be maintained at a higher level without these side effects.

In conclusion, this investigation indicates that patients with stable angina pectoris show a similar frequency of angina, nitroglycerin consumption, and exercise time to moderate angina when taking propranolol, standard formulation pindolol, and slow-release pindolol. The resting heart rate is higher with both forms of pindolol than with propranolol, although exercise values for heart rate at moderate angina are similar with propranolol and the 2 formulations of pindolol.

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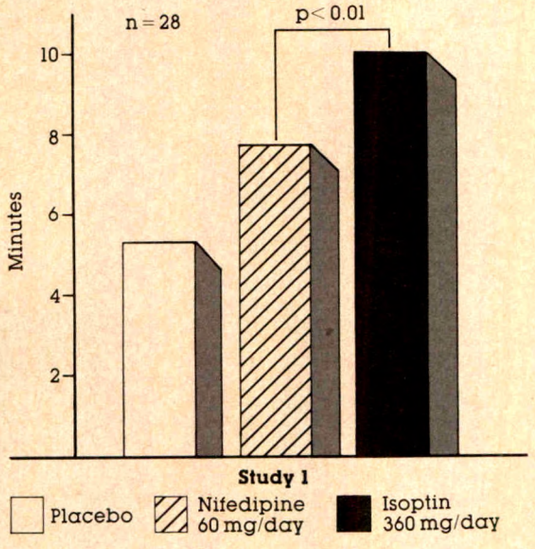

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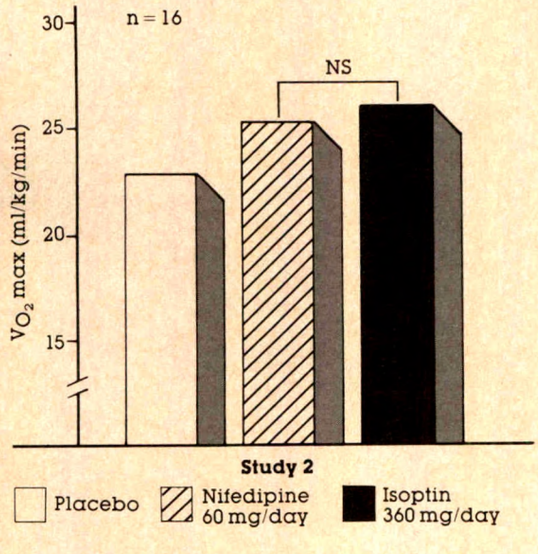

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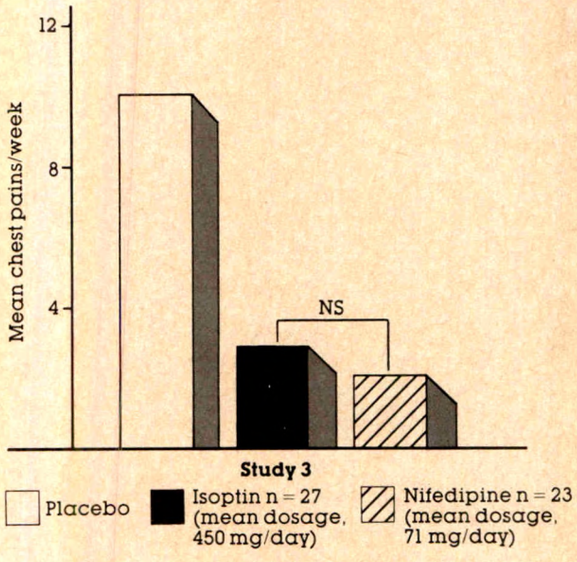

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Please see next page for brief summary of prescribing information.

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Isoptin is contraindicated in severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), and second- or third-degree AV block.

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July 1982 2068

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Frequency and Importance of Unprovoked Coronary Spasm In Patients With Angina Pectoris Undergoing Percutaneous Transluminal Coronary Angioplasty

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Coronary spasm superimposed on fixed coronary artery stenosis was discovered in 14 of 74 candidates for percutaneous transluminal coronary angioplasty (PTCA). In 3 of the 14, spasm developed during PTCA and was presumably catheter-induced. Eleven of the 14, with unprovoked spasm, are the subject of this study. Three of the 11, in whom the fixed component of the mixed stenosis was subcritical, were treated medically, with good results in 2 but with persistent angina pectoris and eventual myocardial infarct in 1. Nitroglycerin administered by the intracoronary route relieved spasm resistant to sublingual nitroglycerin in 1 of the 3. In 8 of the 11 with critical fixed stenosis, spasm was discovered either before PTCA (7 patients) or on follow-up (1 patient). Six of the 8 had successful PTCA, with no or mild symptoms on follow-up. Of the 2 failures, 1, uncomplicated, was followed by successful elective coronary artery bypass surgery while the other, complicated, led to successful emergency coronary artery bypass surgery, with disappearance of symptoms in both. The rate of success was similar in patients with documented unprovoked spasm (6 of 8) and patients without (39 of 63, 62%). It is concluded that (1) coronary spasm, if properly sought for, is probably not uncommon in single-vessel candidates for PTCA; (2) patients considered candidates for PTCA should have intracoronary nitroglycerin administered before PTCA; (3) in patients with critical, fixed coronary artery disease, associated spasm does not reduce the chances of successful PTCA; (4) coronary spasm may outlast the relief by PTCA of the fixed component of the mixed stenosis and requires long-term vasodilator therapy; and (5) the lack of adverse effects when PTCA is performed in patients with spasm superimposed on critical fixed single-vessel stenosis appears to justify its use for the time being.

The existence of vasospastic angina pectoris is well established.[1,2] Coronary spasm may occur at a site with no detectable fixed stenosis or may coexist with any degree of fixed obstruction.[3]

In the context of percutaneous transluminal coronary angioplasty (PCTA), coronary spasm occupies a position of particular interest for 3 main reasons: (1) by location, focal character, and symmetry it mimics the very type of fixed coronary stenosis considered ideal for PTCA; (2) being unpredictable, it may occur during PTCA and possibly affect its immediate results; (3) being recurrent, it can be expected to outlast relief of the fixed component of a mixed stenosis, reproducing blockage and symptoms at a later time. The practical importance of these issues would be marginal if coronary spasm were rare in candidates for PTCA. However, our previous experience suggested that coronary spasm is easily overlooked and might be common in patients with isolated single-vessel stenosis. If spasm were in fact common among candidates for PTCA, it would be of considerable interest to discover the possible reasons for this common association.

A prospective study was designed to achieve the following goals: (1) to unmask spontaneous coronary spasm, when present during diagnostic angiography, in potential candidates for PTCA and establish its prevalence in patients with single-vessel disease deemed amenable to coronary angioplasty; (2) to discover to what extent this prevalence may result from the special composition of the PTCA population; (3) to determine the influence of coronary spasm on the immediate re-

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sults and complications of PTCA; (4) to observe the possible long-term effect of coronary spasm associated with critical, fixed stenosis in patients successfully treated with PTCA.

Methods

The following protocol was established for the detection of *spontaneous* coronary spasm during diagnostic cardiac catheterization in our institution. In all patients aged ≤60 years with a history of angina pectoris of ≤1 year in duration, antiplatelet agents were discontinued at least 1 week, and long-acting nitrates at least 12 hours before the study. No patient was receiving calcium-channel blocking agents at the time of the study. Premedication consisted of oral phenobarbital sodium and diphenhydramine hydrochloride, 50 mg each, in 36 patients, or oral diazepam, 10 mg, in 10 patients. Coronary angiography was carried out both before and after the intracoronary injection of 100 to 200 μg of nitroglycerin. All patients in this group who were found to have single-vessel disease without spontaneous spasm, met the proper criteria (proximal, critical, noncalcified stenosis), and gave informed consent (39 patients) underwent PTCA at a later date. Patients with single, fixed lesions and superimposed spasm (7 patients) were treated medically (3 patients) unless the fixed component was critical (≥60% reduction of normal luminal diameter). Twenty-eight patients were referred for PTCA after coronary angiography done elsewhere. Some were aged >60 years or gave a history of angina pectoris for longer than 1 year. Precise information on the type and time of discontinuation of antiplatelet and coronary vasodilating drugs before the initial diagnostic angiography is not available in these patients. Premedication varied according to referring center, consisting of diazepam, diphenhydramine, or phenobarbital sodium alone or in combination. Nitroglycerin was administered orally before coronary angiography in 5. One patient (Patient 10 of the present series) had spontaneous variation of coronary diameter during diagnostic angiography. In these 28 patients, angiography was repeated before and after intracoronary nitroglycerin on the day of PTCA, before PTCA was attempted. In 2 (Patients 2 and 8 of this series), spasm was first demonstrated at that time. Thus, spontaneous coronary spasm was detected before PTCA in 10 patients. In 1 of the 39 patients initially studied by us, spasm was disco ered for the first time on angiography repeated shortly aft PTCA because of recurrent symptoms. The cardiac medic tion before PTCA in all 74 patients consisted only of lon acting nitrates which were discontinued at least 12 hours b fore PTCA except in Patient 9. During PTCA, 200 μg bolus of intracoronary nitroglycerin were given before, during, an after dilating catheter manipulation in all patients.

All angiograms from our institution and elsewhere wer carefully reviewed for visual evidence of diameter changes a the site of stenosis. In 15 patients, a significant variation wa deemed to be present on inspection. This was confirmed b measurement in 11 patients; in 4 the subjective impression wa not borne out by quantitative analysis. The objective diagnos of coronary spasm was made when the measured average degree of stenosis on the angiogram decreased by ≥20% of th adjacent normal lumen diameter or when a totally occlude vessel reopened to any extent (Patient 9) either spontaneousl or after intracoronary nitroglycerin, or when a stenosed vess developed transient total occlusion (Patient 6). Each angio gram was analyzed independently by 2 of us (LGB and LRL Measurements were made on the frames with the most an least severe stenosis in 2 projections* and averaged. Thus, fo each of the 2 states—spasm and no spasm—the results rep resent the mean of 8 measurements. Measurements were mad directly on the screen of a model XR-35 Vanguard projecto using a magnifying glass with metric grid. The 20% minima significant difference was chosen for consistency with th value adopted by the National Heart, Lung, and Blood In stitute Executive Committee on PTCA to define success whe using this technique. However, the maximal difference be tween the means of 4 measurements made 3 months apart i each of 10 control angiograms was <10% for both co-au thors.

The following clinical definitions have been employed t classify patients in this series: *Stable angina pectoris:* pre dictable, exertional chest pain with no or slow progressio after its inception, without episodes at rest or during sleep *Unstable angina pectoris:* (1) chest pain of recent origin (≤ months) with episodes at rest or during sleep, regardless of th type of initial clinical presentation; (2) chest pain of > months' duration but with recent episodes at rest or durin sleep. *Variant angina pectoris:* chest pain of variable duratio at rest with transient S-T segment elevation in the leads facin the myocardial zone subserved by the stenosed coronary ar tery, responding quickly to nitroglycerin. *Intermediate syn drome:* 1 or more episodes of prolonged chest pain (≥2(minutes) usually with transient ST-T changes, no new Q waves or enzymes elevations, and incomplete response to ni troglycerin. *Subendocardial myocardial infarction:* prolonge episodes of chest pain (≥30 minutes) associated with evolving sustained ST-T changes but no new Q waves, and significan cardiac enzyme elevations. The significance of differences fo variables between patients with and without coronary artery spasm was assessed using the chi-square test and the unpaired Student's *t* test.

TABLE I Clinical Data in 11 Patients With and 63 Patients Without Demonstrated Coronary Spasm

	Spasm Group	No Spasm Group	p Value
Patients (n)	11	63	
Age (yr)	31–63 (48)	31–69 (53)	<0.01
Sex (male/female)	7/4	51/12	NS
Duration of symptoms (mo)	0–36 (7)	0–144 (10) 0–48 (7)*	NS
Type of symptoms			
Stable AP	0/11	9/63	NS
Unstable AP	3	35	...
Variant AP	2	1	...
Intermediate syndrome	4	3	...
Subendocardial MI	2	5	...
Transmural MI	0	10	...
ADA/RCA†	9/2	42/18	NS
Success/total number of PTCA	6/8	39/63	NS
Complications/total number of PTCA	1/8	8/63	NS

* Patient with 144 months' duration of symptoms left out.

† Ratio of anterior descending to right coronary artery stenosis. Three patients in the no spasm group with circumflex artery stenosis are left out.

AP = angina pectoris; MI = myocardial infarction; NS = not significant. For definitions, see the Methods section.

Results

Eighty-two patients were admitted to the Medica College of Pennsylvania for the performance of PTCA as of March 31, 1982. Eight had stenosis of 1 or more saphenous vein grafts and were excluded from this se ries. The remaining 74, 58 men and 16 women aged 31

* Usually 30° right anterior oblique and 45° to 50° left anterio oblique projection with 30° craniocaudal rotation for the left coronary artery, and 30° right anterior oblique and 35° to 40° left anterior oblique projection for the right coronary artery.

to 69 years (mean 51), all with single-vessel disease, are the subjects of this report. Fourteen (19%) had evidence of coronary spasm associated with fixed stenosis. In 3 patients, spasm developed only during PTCA presumably from irritation caused by the dilating catheter; they are included in the subgroup without spontaneous coronary spasm. Eleven patients constitute the coronary spasm subgroup proper. Their age, sex, duration of symptoms, type of angina pectoris, and coronary artery involved are given in Table I. PTCA was carried out in 8 by the technique of Grüntzig et al,[4] while 3 in whom the fixed component of the mixed stenosis was noncritical were treated medically. In 63 patients, spontaneous coronary spasm was not apparent; all underwent PTCA. Table I shows that the composition of the subset with spontaneous coronary spasm did not differ from the subset without spasm except for age.

Coronary spasm superimposed on subcritical fixed stenosis (Patients 1 to 3): There were 3 patients in this group, with mixed (fixed plus spastic component) stenosis of 80, 66, and 70%, respectively of the left anterior descending artery which decreased to 45, 30, and 23% of the luminal diameter after intracoronary nitroglycerin. No chest pain developed during diagnostic angiography in any of these patients. All were treated medically with nitrates and nifedipine. Patients 1 and 2 have been followed up for 35 and 10 months, respectively, with no recurrence of chest pain in the former and rare and mild episodes in the latter. In Patient 3, the attacks of angina pectoris worsened despite medication and he had an inferior myocardial infarction 6 months later. Repeat coronary angiography disclosed de novo occlusion of the previously unobstructed right coronary artery and progression of the fixed component of the left anterior descending stenosis from 23 to 62%. Coronary artery bypass surgery to the left anterior descending and right coronary arteries was carried out. Thirteen months later, the patient has occasional mild episodes of chest pain at rest despite administration of nitrates and nifedipine.

Critical (>60%) fixed stenosis: Superimposed spasm before PTCA or on follow-up (Patients 4 to 11): There are 8 patients in this group; in 7 (Patients 4 to 10) spasm was documented before PTCA and in Patient 11 it was documented on follow-up. In Patients 4 and 5, mixed stenoses of 90 and 82% (Fig. 1, top left)

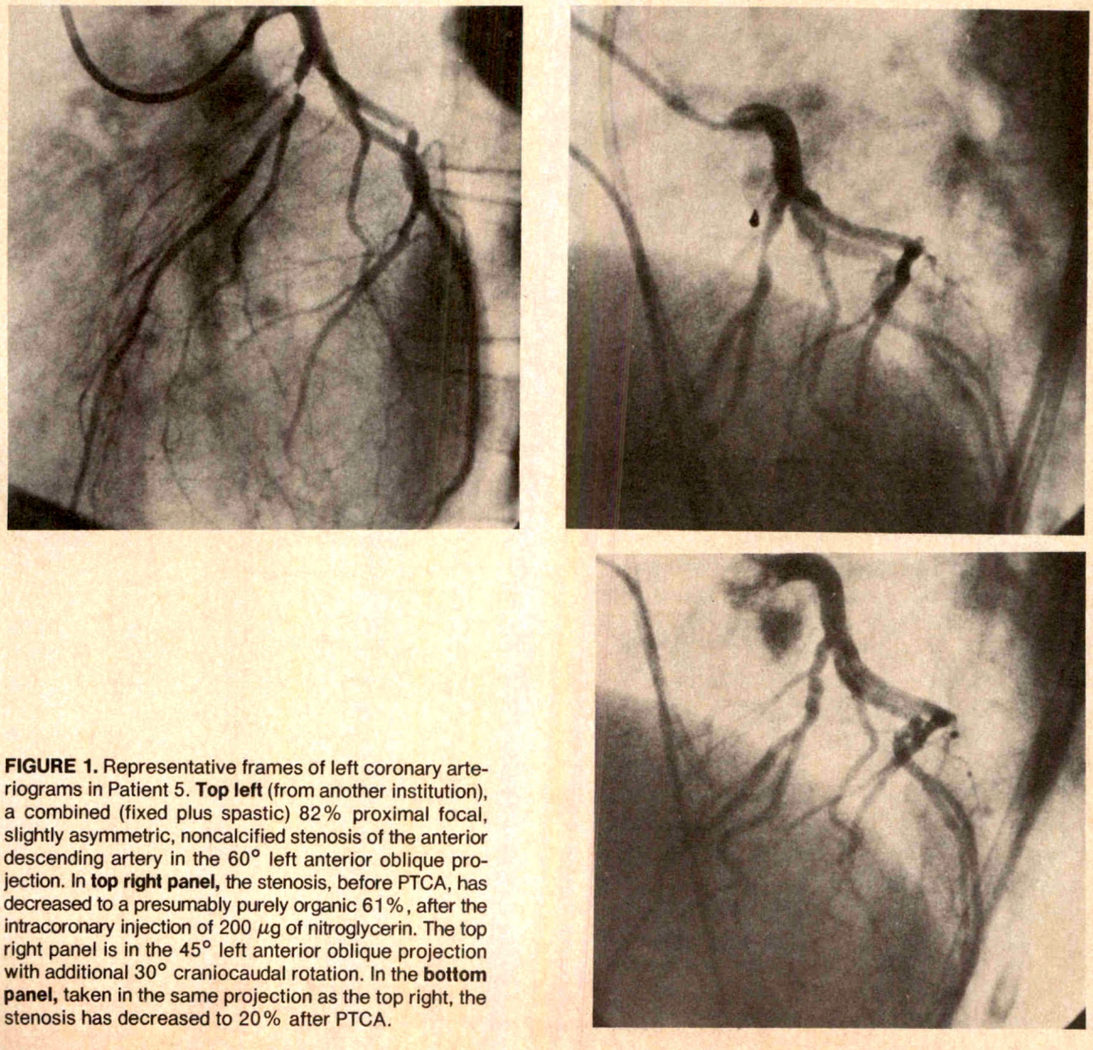

FIGURE 1. Representative frames of left coronary arteriograms in Patient 5. **Top left** (from another institution), a combined (fixed plus spastic) 82% proximal focal, slightly asymmetric, noncalcified stenosis of the anterior descending artery in the 60° left anterior oblique projection. In **top right panel,** the stenosis, before PTCA, has decreased to a presumably purely organic 61%, after the intracoronary injection of 200 μg of nitroglycerin. The top right panel is in the 45° left anterior oblique projection with additional 30° craniocaudal rotation. In the **bottom panel,** taken in the same projection as the top right, the stenosis has decreased to 20% after PTCA.

of the left anterior descending artery decreased to 66 and 61%, respectively (Fig. 1, top right) after intracoronary nitroglycerin, and were further reduced to 40 and 20% (Fig. 1, bottom) after PTCA. In Patient 6, a 90% fixed stenosis of the right coronary artery became totally occluded during diagnostic angiography, and had prompt response to intracoronary nitroglycerin; it decreased to 32% after PTCA. In Patient 7, a mixed, 68% left anterior descending stenosis decreased to 26% after intracoronary nitroglycerin but was found to have become fixed at 78% on repeat catheterization performed because of recurrent symptoms despite nitrates and nifedipine. Percutaneous transluminal coronary angioplasty reduced the fixed stenosis to 17%. Patient 8 had crushing chest pain with marked S-T segment elevation in V_1–V_3 on the day of PTCA while on the catheterization table but before catheter insertion. Sublingual nitroglycerin quickly terminated the attack. Percutaneous transluminal coronary angioplasty reduced the fixed left anterior descending stenosis from 61 to 19%. Patient 9, with intermediate syndrome, was found on diagnostic angiography to have 100% occlusion of the right coronary artery which decreased to 90% after intracoronary nitroglycerin and further to 80% after the intracoronary administration of 300,000 units of streptokinase. One week later, during attempted PTCA, the stenosis was 60%. The procedure was complicated by intimal dissection, with chest pain and S-T segment changes. Emergency coronary artery bypass surgery was successful but a transmural inferior myocardial infarction developed. Patient 10 had spontaneous variation of a mixed left anterior descending stenosis between 68 and 92% on diagnostic angiography done elsewhere. During unsuccessful PTCA, he had 100% occlusion of the left anterior descending artery with moderate chest pain. Intracoronary nitroglycerin restored flow, and he later underwent elective uneventful coronary artery bypass surgery. Patient 11, with atypical angina pectoris and a previous subendocardial myocardial infarction, had successful reduction by PTCA of a seemingly purely organic 70% left anterior descending stenosis to 30%. Shortly thereafter, atypical angina pectoris resumed despite oral nitrates. Repeat angiography revealed a 70% stenosis at the site of PTCA which decreased to 40% after intracoronary nitroglycerin. In addition to Patients 8 and 10, chest pain was present during part of angiography in Patients 6 and 9 but subsided after intracoronary nitroglycerin; Patients 4, 5, 7, and 11 remained asymptomatic.

The follow-up in this group ranges from 6 to 31 months (mean 17). Except for Patients 9 and 10, all others have been receiving nitrates and nifedipine. There has been complete suppression of angina pectoris in Patients 6 to 8. In Patients 4, 5, and 11, rare and mild episodes of chest pain occur despite medication. In Patient 5, repeat angiography showed no progression of the residual stenosis at the site of PTCA. However, diffuse spasm of the right coronary artery was discovered which reduced the lumen by 61% and was promptly relieved by intracoronary nitroglycerin. Patients 9 and 10, 9 and 12 months postoperatively, have no symptoms and are taking no cardiac medication.

Discussion

Coronary artery spasm can be recognized angiographically by transient variation in segmental luminal diameter. For detection, frames with and without spasm must be compared. Grading by visual inspection has been shown to be hazardous due to large intra- and interobserver error.[5–8] However, quantitative grading of the subjectively chosen vessel borders has proven precise and reproducible[9–11]: for vessels of ≥3 mm diameter—the size of proximal coronary arteries in humans—the mean observer error is about 5%[9,10] with a maximal error of 11% in 1 series.[11] To be acceptable, the minimal diagnostic change in vessel diameter must exceed the maximal measuring error. The minimal 20% difference in luminal diameter chosen as diagnostic of spasm in the present series far exceeds the maximal error made by each of 2 co-authors in 10 control angiograms. A second type of error could be incurred, independent of inaccuracies in measurements. Nitroglycerin has a vasodilating effect in organically stenosed as well as normal coronary artery segments in vivo.[12] Ignorance of this effect could lead to incorrect labeling of the physiologic relaxation of vascular tone at the site of stenosis after intracoronary nitroglycerin as relief of spasm. In a recent report,[12] the cross-sectional area at the site of severe organic stenoses comparable to what was found in most patients in this series increased by as much as 36% after sublingual nitroglycerin administration, corresponding to a diameter increase of 16.5%. However, when the ratio between obstructed and normal coronary segments was employed, as done by us, the percent stenosis was the same both before and after nitroglycerin because diseased and normal segments dilate proportionately.[12] From the foregoing considerations we are confident that the diagnosis of coronary spasm was correct in all patients of this series. Figure 1 provides the visual verification of the smallest percent change in luminal diameter (21%) in our patients.

Coronary spasm is transient and unpredictable and may affect the outcome of PTCA, hence the need for its recognition. When present at the beginning of angiography, spasm can be unmasked by repeated visualization after coronary vasodilators; when initially absent, it can be detected by spontaneous or induced development during the study. Sublingual nitroglycerin may fail to relieve preexistent coronary spasm. Thus, for maximal sensitivity, we advocate the intracoronary route.[13] Although we are not aware of failures to unmask it using this approach, the possibility cannot be excluded. The spontaneous development of spasm is easily detected by reduction in lumen diameter during the sequential coronary injections. When absent during coronary angiography, coronary spasm can be induced by provocative testing.[14,15] However, because of the attendant risks,[16,17] we are reluctant to use provocative testing in patients with high-grade fixed stenosis.

The 15% incidence of unprovoked coronary spasm in this series is higher than we expected. Even so, this percentage probably represents only its random occurrence in our population at a given time, as opposed to true prevalence which may be higher. The mixed

obstruction spasm produces in these patients is often subtotal and asymptomatic.

Is there a possible explanation for the relatively large number of patients with coronary spasm among our candidates for PTCA? Evidence is mounting that coronary spasm plays a significant role in the pathogenesis of chest pain in all the unstable angina pectoris syndromes by causing a transient reduction or interruption of coronary blood flow while myocardial oxygen demand remains stable.[3,18,19] The majority of patients in this series, 65 of 74, had some form of unstable angina pectoris or had acute myocardial infarction after an unstable course; the discovery of spontaneous coronary spasm in 11 is not surprising. It is possible that, had provocative tests been carried out, more cases of spasm might have been discovered. Thus, the high incidence of coronary spasm probably just reflects the high prevalence of unstable angina pectoris in our series. This, in turn, may result in part from the selection criterion for PTCA recommending a duration of angina pectoris of ≤1 year.[4] This criterion favors clustering of patients with angina pectoris of recent onset, 1 form of unstable angina pectoris, among candidates for this procedure. On this basis, we would expect a relatively high prevalence of coronary spasm in other PTCA laboratories as well.

The demonstration of coronary spasm superimposed on a fixed stenosis has been thought to represent a relative contraindication to the performance of PTCA.[20] This has been based on several lines of reasoning. Historically, the supposedly adverse influence of a spastic "diathesis" on the results of coronary artery bypass surgery in patients with Prinzmetal's angina and mixed stenoses has been stressed,[21] although not without subsequent challenge.[22,23] More pertinently, 1 late death in the original report by Grüntzig et al[4] and 2 early deaths in the National Heart, Lung, and Blood Institute registry[24] may have been caused by spasm. The present series reveals a 75% (6 of 8) success rate in patients with spasm and a 62% (39 of 63) success rate in patients without it, suggesting that spasm does not reduce the chance of early success. The rate of complications requiring emergency coronary artery bypass surgery is similar in patients with spasm (1 of 8, or 13%) and without spasm (8 of 63, or 13%).

Because of its propensity to recur, coronary spasm has obvious relevance to the long-term follow-up of patients in this series. The follow-up of the 3 patients treated medically with nitrates and nifedipine because of a subcritical organic component of a mixed stenosis indicates that, although usually effective, coronary vasodilators cannot totally prevent the recurrence of angina pectoris and the development of complications in this subset of patients. The 6 patients treated successfully by PTCA have all received nitrates and nifedipine. Three of the 6 are asymptomatic while in the other 3 rare, mild episodes of atypical chest discomfort persist, qualitatively similar to the attacks before PTCA. In 2 of the latter 3 patients, the persistence of coronary spasm has been documented, in 1 of them in a different artery than the 1 successfully dilated. Thus, while the critical fixed component of a mixed stenosis may be relieved, spasm may recur and warrants long-term use of nitrates and calcium blockers. The 2 patients who underwent coronary artery bypass surgery after unsuccessful PTCA remain asymptomatic without vasodilator medication. Spasm therefore has not adversely affected the long-term results of coronary artery bypass surgery in these 2 patients.

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Assessment of Plexectomy in the Treatment of Severe Coronary Spasm in Patients With Normal Coronary Arteries

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Surgical denervation of the heart by plexectomy was performed in 3 patients with variant angina, documented coronary spasm, and normal findings on coronary angiography. In all cases, spasm had already been responsible, preoperatively, for myocardial infarction and recurred thereafter in another territory despite medical therapy with a combination of nitrates and calcium antagonists. Plexectomy was performed using a standardized technique. The effectiveness of surgical suppression of cardiac autonomic innervation was confirmed postoperatively by pharmacologic tests. In 2 patients inferior myocardial infarction developed in the early postoperative period; in the third patient, coronary spasm recurred 3 weeks after plexectomy. Thus plexectomy, despite an adequate suppression of autonomic innervation, was ineffective in all cases and may even have been harmful in 2 patients. These data contradict the good results obtained by plexectomy associated with aortocoronary bypass in patients with variant angina and fixed stenotic coronary arteries. This discrepancy may be accounted for by a different pathophysiologic mechanism of vasospasm in normal coronary arteries and in diseased arteries at the site of the atheromatous stenosis. Thus, plexectomy should not be considered in the treatment of vasospasm involving normal coronary arteries, even if medical therapy fails to achieve satisfactory control of variant anginal attacks.

The introduction of calcium antagonists has provided a satisfactory means of preventing variant angina attacks in most patients with coronary spasm and normal coronary arteries.[1–3] However, in a limited number of patients, recurrence of coronary spasm cannot be controlled medically and may lead to myocardial infarction (MI) or sudden death.[3–5] In some patients with Prinzmetal's variant angina, the role of the autonomic nervous system in the pathophysiology of coronary spasm has been well established[6,7]; surgical suppression of the cardiac autonomic nervous system has therefore been advocated by several investigators in the treatment of this syndrome.[8–13] Experience with this procedure is limited, however, and the available results are contradictory. Some workers report good results when denervation is associated with coronary artery bypass grafting (CABG) in patients with coronary spasm and significant organic stenosis[10]; others have had poor results, high operative mortality rates, and recurrence of spasm when denervation was performed alone or in association with CABG.[12] These conflicting findings could be explained by differences in patient selection and operative procedure. In this report, we describe the results of cardiac denervation by plexectomy in 3 patients with severe variant angina refractory to maximal medical therapy. All 3 patients had normal coronary angiograms, and spasm was therefore the sole cause of myocardial ischemia. Postoperatively, the 3 patients

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underwent pharmacologic testing to prove full suppression of the autonomic cardiac innervation and to therefore confirm a uniform surgical outcome.

Patients Studied

Plexectomy was considered only when maximal medical therapy failed to control attacks of variant angina. In all 3 patients, despite medical treatment, coronary spasm had already provoked MI and occurred thereafter in another vascular territory. We used the operative procedure described by Bertrand et al.[10] A continuous intravenous infusion of nitroglycerin was begun before surgery. All patients were receiving nifedipine, and the drug was continued during the perioperative period. A bolus of lidocaine was infiltrated under the aortic root to avoid a possible spasm induced by the manipulation of Wrisberg's ganglia. Then, using the 3-step procedure described by Bertrand et al, as much as possible of the major cardiac plexus, including the nerves to the right coronary artery, was resected.

Case 1: A 34-year-old man had severe chest pain at rest accompanied by a 3 mm S-T segment elevation in leads D_2, D_3, and Vf. Sublingual nitroglycerin relieved pain and the electrocardiogram returned to normal. Nifedipine (20 mg) and isosorbide dinitrate (20 mg) were administered orally, but 1 hour later chest pain recurred, accompanied by S-T segment elevation in leads V_1 to V_4. Despite intravenous nitroglycerin, an anterior myocardial infarction (MI) developed. Coronary angiography was performed 1 week later while the patient was receiving nifedipine and isosorbide dinitrate. Left ventriculography showed signs of anterior hypokinesia and a depressed ejection fraction (35%). The left coronary angiogram was normal. During right coronary catheterization, chest pain occurred with S-T segment elevation in leads D_2, D_3, and Vf; on right coronary angiography an 80% narrowing of the midportion of the right coronary artery was observed, and was reversed by intravenous nitroglycerin. Four hours after plexectomy while 35 μg/min of nitroglycerin was being infused, S-T segment elevation in inferior leads D_2, D_3, and Vf occurred and was soon followed by second-degree atrioventricular block. Despite increasing the nitroglycerin infusion rate to 60 μg/min and administration of sublingual nifedipine, spasm could not be reversed and the patient had an inferior MI. Necrosis was complicated by severe acute left ventricular failure. During the following days no chest pain was noted and Holter monitoring showed no asymptomatic S-T segment modification. The patient had chronic left ventricular failure and is presently in New York Heart Association class III.

TABLE I Results of Pharmacologic Testing

	Case 1		Case 2		Case 3	
	HR (beats/min)	SBP (mm Hg)	HR (beats/min)	SBP (mm Hg)	HR (beats/min)	SBP (mm Hg)
Phenylephrine (μg/min)						
0 (baseline)	96	145	89	126	93	139
50	97	150	87	132	92	141
100	93	178	88	155	90	164
200	94	195	85	182	91	186
Atropine						
Baseline	94	140	88	131	91	141
Maximal value during 30 min	99	148	94	134	95	145

HR = heart rate; SBP = systolic blood pressure.

Case 2: A 51-year-old man had episodes of nocturnal chest pain during 1 week; after 1 episode which lasted over an hour, electrical signs of anteroseptal MI were recorded. The patient was admitted to the coronary care unit, where attacks of Prinzmetal's variant angina recurred despite administration of nifedipine (80 mg/day) and intravenous nitroglycerin, with transient S-T segment elevation involving either the anterior leads V_1 to V_4 already involved in the MI or the inferior leads. Both left and right coronary arteries were normal at angiography. Left ventriculography showed limited anteroapical akinesia; the ejection fraction was moderately reduced (45%). Twelve hours postoperatively, S-T segment elevation occurred in inferior leads D_2, D_3, and Vf and could not be reversed by increasing the nitroglycerin infusion rate from 20 to 50 μg/min or by administrating sublingual nifedipine. Inferior MI developed. Recovery was uneventful. Subsequently, the patient received nifedipine, 80 mg/day, and 80 mg/day of isosorbide dinitrate; no recurrence of variant angina was noted and Holter monitoring showed no asymptomatic S-T segment change.

Case 3: A 47-year-old woman was admitted to the coronary care unit 3 hours after the onset of chest pain. Electrocardiography showed inferior MI; her recovery was uneventful. Coronary arteriography was performed 3 weeks later while the patient was receiving nifedipine, 60 mg/day, and 60 mg/day of isosorbide dinitrate. Left ventriculography showed inferior akinesia, and the ejection fraction was 52%. After ventriculography, chest pain developed and S-T segment elevation was recorded in precordial leads. The left coronary angiograms showed stenosis of the proximal part of the left anterior descending artery. This stenosis was completely reversed by the intravenous administration of nitroglycerin. The right coronary artery was normal. Plexectomy was performed thereafter and the postoperative period was uneventful; the patient was discharged on the 11th postoperative day with nifedipine, 60 mg/day. Two weeks later the patient had chest pain, and electrocardiographic monitoring recorded transient S-T segment elevation in the inferior leads, already involved in the previous MI. High-dose isosorbide dinitrate and nifedipine controlled the symptoms of variant angina. The patient remained symptom-free thereafter, and repeated Holter monitorings showed no S-T modifications.

Control of the Suppression of Autonomic Command of the Heart

Autonomic nerve fibers were found in all resected tissues submitted for histologic examination; however, these findings indicate only that some of the cardiac nerves were resected and cannot establish that all physiologically significant innervation was suppressed.

Since no perioperative criteria can establish that all physiologically significant cardiac nerves had been resected, all 3 patients underwent pharmacologic assessment of autonomic control of the heart. This procedure was performed within 2 to 3 weeks after surgery. In order to evaluate the bradycardic baroreceptor reflex response to an increase in arterial pressure, a phenylephrine infusion was administered. Phenylephrine, a vasoconstrictive alpha-adrenergic receptor agonist, was infused at increasing rates from 50 to 200 μg/min to increase blood pressure. Infusion rates were doubled every 5 minutes. The electrocardiogram was monitored during the infusion to determine heart rate. Denerva-

tion was considered satisfactory if no significant reflex bradycardia (>5% of baseline value) was noted. Atropine was also used to assess the effectiveness of parasympathetic suppression. After the phenylephrine infusion and the return of arterial pressure to baseline values, an intravenous bolus of 0.02 mg/kg of atropine was administered. The electrocardiogram was monitored over the following 30 minutes. Denervation was considered effective if no significant increase (<5% of the baseline value) in heart rate occurred.

The results of the pharmacologic testing are summarized in Table I. The increase in arterial pressure elicited by phenylephrine provoked no significant reflex bradycardia, and atropine induced no significant increase in heart rate. These findings indicate suppression of the autonomic control of the heart.

Discussion

In our 3 patients, despite the satisfactory surgical suppression of autonomic innervation of the heart, plexectomy failed to prevent recurrent coronary spasm. Moreover, in 2 cases MI occurred in the immediate postoperative period and was probably secondary, in these patients with variant angina and angiographically normal coronary arteries, to occlusive coronary spasm. The cause-and-effect relation between surgical denervation and MI is difficult to establish with certainty in these patients with severe recurrent spasm that had already been responsible for previous MI. Nevertheless, MI in the immediate postoperative period cannot be considered a simple coincidence, and plexectomy may have had deleterious effects in the 2 patients concerned. Our study group includes highly selected patients. In all subjects, spasm was the sole cause of ischemia; coronary arteries were entirely normal at angiography without any significant stenosis. Spasm was extremely severe and had already been in each patient, before surgery was performed, the cause of MI. In all cases, spasm was documented despite medical management with a combination of nitrate and the calcium antagonist nifedipine. Thus, our study group represented patients with the most severe form of vasospasm and cannot therefore be considered representative of the entire population of patients with Prinzmetal's variant angina.

The negative results we present agree with those obtained by Clark et al[12] in 8 patients in whom cardiac denervation was achieved by plexectomy or autotransplantation. Buda et al[13] reported a case of coronary spasm occurring in a patient 2 years after he had received a heart transplant. The absence of reinnervation of the transplanted heart was demonstrated by pharmacologic testing and the spasm involved, as in our 3 patients, the right coronary artery. Bertrand et al[14,15] reported the case of a patient treated by autotransplantation for Prinzmetal's variant angina involving normal coronary arteries. Eighteen months after surgery, chest pain recurred and the electrocardiogram showed signs of variant angina. In contrast to these negative results involving patients with pure spasm, Bertrand et al[10] reported excellent results when plexectomy was associated with CABG in patients with spasm superimposed on significant fixed stenosis. Thus, plexectomy seems to have clearly different results when performed alone in patients with spasm and without coronary narrowing or in association with CABG in patients with significant stenosis. These drastically different results after suppression of cardiac autonomic innervation raise a question about the heterogeneity of the pathophysiology of coronary spasm. The currently proposed mechanisms of coronary spasm include abnormalities of the autonomic control of the heart, local production of vasoconstrictive metabolites, increased levels of circulating vasoactive substances, or increased responsiveness of the coronary arteries to these substances. In a given patient, spasm may be provoked by any one or more of these various mechanisms; moreover, the sequence of pathophysiologic events leading to spasm may vary from one patient to another. It is conceivable that the autonomic nervous system plays the predominant role in producing spasm superimposed on significant coronary stenosis but that vasospasm of normal coronary arteries may be, at least in some patients, independent of any abnormality of the neural control of the heart. Such a difference in pathophysiology would explain the discordant results obtained after plexectomy performed alone on normal coronary arteries or in association with CABG on stenotic arteries. In 2 of our patients, plexectomy may have been responsible for worsening of coronary spasm; a possible explanation for this phenomenon may be the occurrence of a denervation hypersensitivity increasing the vasoconstrictive response of the coronary artery to circulating catecholamines. It should be noted that in all 3 cases, postoperative coronary spasm involved the right coronary artery.

Suppression of the vasodilator parasympathetic tone of the right coronary artery may provide the explanation for the observed events. It is well established that the parasympathetic neuromediator acetylcholine causes the release of norepinephrine by the postganglionic sympathetic nerve fiber.[16,17] Norepinephrine, through its action on the coronary artery alpha-adrenergic receptors, induces vasoconstriction. Thus, by indirect effect, the parasympathetic tone is involved in coronary vasoconstriction. However, the direct effect of parasympathetic stimulation is coronary vasodilation mediated by muscarinic acetylcholine released by the postganglionic parasympathetic nerve ending.[18] The right coronary circulation may be physiologically more sensitive to the direct cholinergic vasodilatation and therefore may become more susceptible to the action of local or circulating vasoconstrictive metabolites once plexectomy is performed.

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Effects of Early Postmyocardial Infarction Exercise Testing On Self-Perception and Subsequent Physical Activity

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The effects of exercise testing 3 weeks after clinically uncomplicated myocardial infarction (MI) on subsequent physical activity were evaluated in 40 consecutive men with a mean age of 52 ± 9 years. Patients' confidence in their ability to perform various physical activities was evaluated with self-efficacy scales which patients completed before and after a symptom-limited treadmill exercise test. Increases in confidence (self-efficacy) for activities similar to treadmill exercise (walking, stair climbing, and running) were greatest after treadmill exercise, whereas increases for dissimilar activities (sexual intercourse and lifting) were greatest after test results were explained by a physician and nurse. The intensity and duration of subsequent physical activity at home were more highly correlated with self-efficacy after treadmill exercise than with peak treadmill heart rate. Of the 8 patients whose treadmill tests were limited by angina pectoris, 7 had self-efficacy scores which remained low after treadmill testing or which decreased from initially high values after treadmill testing. These patients had lower peak heart rates and work loads than patients whose self-efficacy increased or remained high after treadmill testing. After MI, patients' perception of their capacity for physical activity and their actual patterns of subsequent physical activity are influenced by early treadmill testing in a manner which is congruent with these patients' treadmill performance.

Patients often fear physical activity after clinically uncomplicated myocardial infarction (MI) and may limit or postpone their usual activities, including occupational work, until long after it is medically safe to resume them. Standard psychological tests, such as the Minnesota Multiphasic Personality Inventory, do not permit the identification of patients whose concerns about physical activity levels may be medically unwarranted: these test methods yield global assessment of psychological status or symptoms which are poorly correlated with discrete behaviors such as return to work.[1]

Scales have been developed to study the relation between self-perceived efficacy (confidence) and behavior. While an individual's self-efficacy judgments may vary from 1 activity to another, the level of self-efficacy reliably predicts whether a particular activity will be attempted.[2] We considered that self-efficacy scales might reliably measure the increased confidence in the ability to resume usual postinfarction activities that is observed in patients performing treadmill exercise soon after clinically uncomplicated MI.

The present study had 3 major goals: (1) to determine the correspondence between pretreadmill self-efficacy and treadmill performance, (2) to measure changes in self-efficacy resulting from treadmill testing and subsequent counselling by a physician and nurse, and (3) to determine whether subsequent physical activity in the normal environment was more closely related to exercise performance or to self-efficacy after exercise testing.

Methods

Patients who were free of unstable angina pectoris and clinical heart failure, including an S_3 gallop 3 weeks after MI, were eligible to undergo treadmill exercise testing. Forty consecutive men (mean age 52 ± 9 years) participated in this project; 90% of the patients were married and most were of middle or upper middle socioeconomic status.

The overall design of the study is depicted in Table I. Before treadmill testing, patients were asked to complete a set of

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TABLE I Measurement of Self-Efficacy and Physical Activity

Days After MI	Sequence of Events*
18–20	3-day activity record
21	SE_1/TM/SE_2/counselling/SE_3
25–28	3-day activity record

* For the 18 patients who completed activity logs and for all patients during the day of the treadmill test (TM). SE = self-efficacy scale.

questionnaires including a demographic information form, measures of depression (Beck et al,[3] Hamilton[4]) anxiety (Spielberger et al[5]), and marital adjustment (Locke-Wallace[6]) and self-efficacy. A set of 6 self-efficacy scales was developed to measure patients' self-perceived ability to carry out the following activities: (1) walking, (2) running distances ranging from 1 block to 5 miles, (3) climbing stairs for distances from a few steps to 4 flights, (4) engaging in sexual intercourse (not including foreplay) from 1 to 20 or more minutes, and (5) lifting objects weighing 10 to 75 pounds (4.5 to 34 kg). A sixth item requested an overall estimate of ability to tolerate physical exertion on a 6-point scale ranging from "very light" to "extremely hard." Patients were asked to indicate whether or not they thought they could perform a given level of activity and to record their level of confidence in this judgment. Confidence estimates were made on a scale which ranged from 10 (quite uncertain) to 100 (completely certain). A similar methodology was used by Bandura[7] and others in previous studies of self-efficacy. Self-efficacy estimates do not change with repeated testing in the absence of interventions.[7,8]

A patient's self-efficacy score for a given task (such as running) was the sum of the confidence estimates the patient gave for successive levels of the task (for example, run 1 block, run 2 blocks, run 5 blocks) divided by the number of levels on that particular scale (for example, 9 levels for running). Scores were computed for each of the 5 physical tasks and for general exertion ratings. A seventh self-efficacy score, created by summing the scores for running, walking, and climbing, was used to measure the correspondence between postexercise test efficacy estimates and activities in the normal environment.

A subgroup of 18 patients reported their levels of physical activity for 3 days before the exercise test using activity logs that they were given at the time of hospital discharge. On the activity logs, each day was divided into 3 "self-observation" periods: morning, afternoon, and evening. Patients were asked at the end of each of the 3 periods to indicate the most strenuous physical activity they had performed during that period, the duration of this activity, and the peak heart rate attained during the activity. Patients were taught to measure their pulse rate before hospital discharge.

Preliminary studies had indicated that patients were relatively less active on the day after exercise testing than during the following 3 days. Accordingly, activity levels on the 3 days immediately before exercise testing were compared with levels recorded on the same 3 days of the following week.

All patients performed symptom-limited treadmill exercise testing using a modified Balke protocol[9] to endpoints of limiting symptoms or to decrease in systolic pressure of 10 mm Hg or more compared with an earlier stage of exercise. Immediately after the test, patients completed the self-efficacy questionnaire a second time and were interviewed, first by a cardiologist and then by a specially trained nurse. The cardiologist explained the results of the test to the patient in detail and discussed with the patient his capacity to perform various physical activities such as walking, jogging, and stationary cycling. The nurse then reinforced the cardiologist's "clearance" to perform these activities, instructing patients to avoid heart rates exceeding 85% of the highest heart rate at which angina pectoris or ischemic S-T segment depression were absent during exercise testing. After the nurse's interview, patients completed the self-efficacy questionnaires a third time and were given new activity logs.

The accuracy of self-reported activity and heart rate levels was determined by direct physiologic measurement of physical activity and heart rates using a portable solid-state computer (Vitalog).[10] The Vitalog system consists of a CMOS solid-state microcomputer (MC-2) interfaced with a read-only memory and a random-access memory, a motion sensor, and an analog R-wave detector connected to the chest by electrocardiographic electrodes. The microcomputer contains 36 K bits of CMOS random-access memory. The MC-2 measures 4 × 8 × 12 cm, weighs 0.1 kg, and is worn on the belt. The motion sensor, which is attached to the right lateral thigh by tape, consists of 6 liquid mercury tilt switches aligned on the faces of a cube. Movement in any direction causes the switches to open and close. The number of openings and closings each minute is accumulated and stored logarithmically. In a previous study, we found good correspondence between heart rate recorded by the MC-2 and by an ambulatory electrocardiogram and between physical activity levels recorded by the MC-2 and those observed during gradually increasing treadmill work loads.[10] For purposes of the present study, the total number of heart beats recorded per minute was stored.

The monitor was worn during the 3 days on which patients recorded their activity levels before and after exercise testing. The Vitalog was randomly allocated to 10 of the 18 patients who completed activity logs. Clinical characteristics, age, treadmill performance, and self-efficacy of the 18 patients who completed activity logs were similar to those of the 22 patients who did not complete activity logs.

Vitalog records were compared with self-report for each of the 3 daily periods on each of the 3 days. Agreement between self-reported physical activity and that recorded on the MC-2 was determined for moderate and greater levels of physical activity. "Moderate" physical activity on the MC-2 was classified as a combination of heart rate and physical activity intensity which exceeded that observed during the patient's treadmill workload of 4 mets. The duration and intensity of physical activity reported as "moderate" or greater corresponded to that recorded on the MC-2 in 94% of comparisons.

Results

Patients' clinical status, treadmill test performance, and psychologic test scores showed them to be a relatively uncomplicated and comparatively well-adjusted group. Mean scores for depression, anxiety, and marital adjustment did not differ from norms derived from healthy adults.[11] Patients attained an average treadmill work load of 6.1 ± 1.4 mets and an average peak heart rate of 132 ± 15 beats/min. More than two thirds of the tests were stopped because of fatigue and shortness of breath, 20% were stopped because of exertional angina pectoris, and 15% because of a decrease in systolic pressure. No test was discontinued because of cardiac signs (blank faces, staggering gait) or advanced grades of ventricular ectopic activity.

Ten patients had a history of angina pectoris for at least 3 months before MI. Seven patients had angina pectoris in the 7 to 10 days preceding treadmill testing,

and an additional 4 patients had angina for the first time during this interval. The average frequency of anginal attacks was twice weekly in these 11 patients, all of whom received only nitroglycerin for relief of chest pain. No patient received beta blockers or calcium-channel antagonist drugs for treatment of chest pain. In 4 patients who were receiving beta blockers for control of arrhythmia or blood pressure, this medication was discontinued 24 to 36 hours before treadmill exercise. None of these patients had treadmill-induced ischemic S-T segment depression or angina pectoris. Of the 11 patients with angina pectoris before or after infarction, 7 had treadmill angina. Only 1 patient with treadmill angina had neither preinfarctional angina nor angina in the 7 to 10 days preceding the exercise test. Of the 8 patients with treadmill angina, 6 had S-T segment depression; an additional 7 patients had painless ischemic S-T segment depression.

Relation between pretreadmill self-efficacy and treadmill performance: To determine the extent of agreement between self-efficacy judgments and treadmill performance, efficacy scores were correlated with peak treadmill heart rates. Correlations between peak treadmill heart rate and post-treadmill self-efficacy, which approximated $r = 0.5$, were generally higher than between peak treadmill heart rate and pretreadmill self-efficacy, which approximated $r = 0.36$. After exercise testing, scores for all 5 activities and for general exertion increased significantly and were proportionately greater for running, climbing, and general exertion than for walking, sexual activity, or lifting (Fig. 1, cross-hatched portions of vertical bars).

Among patients with low self-efficacy scores before treadmill testing, those who performed well on the test exhibited proportionately larger increases in self-efficacy than those who performed less well (Fig. 2). Of the 20 patients whose pretreadmill self-efficacy scores for running 1 block were below the group mean, 12 performed relatively intense treadmill exercise and 1 of these stopped because of angina pectoris. Self-efficacy scores for running 1 block increased 285% after treadmill exercise in these 12 patients ($p < 0.005$). In contrast, the remaining 8 patients with low pretreadmill self-efficacy scores for running 1 block performed relatively less intense exercise (Fig. 2) and 4 of these 8 were stopped because of exertional angina pectoris. Self-efficacy scores for running increased 130% after treadmill exercise in these 8 patients (not significant [NS]).

Among patients with *high* self-efficacy scores before treadmill testing, those who performed well on the test sustained high values of self-efficacy (+58%), whereas self-efficacy tended to decrease (−33%) in patients who performed less well (Fig. 2). Of the 20 patients whose pretreadmill self-efficacy scores for running 1 block were above the group mean, 15 performed relatively intense treadmill exercise and none was stopped because of angina pectoris. In contrast, the remaining 5 patients of this group with high pretreadmill self-efficacy scores for running 1 block performed relatively less intense treadmill exercise (Fig. 2) and 3 of the 5 were stopped because of exertional angina pectoris.

Thus, patients in whom self-efficacy scores remained low or decreased after treadmill testing, who comprised one third (13 of 40) of the patients, accounted for 88% (7 of 8) of those with limiting angina pectoris. These patients also accounted for 54% (7 of 13) of patients with exercise-induced ischemic S-T segment depression.

Effect of counselling on self-efficacy: The additive effect on self-efficacy of counselling by a physician and a nurse is shown by the clear portions of the vertical bars in Figure 1. After counselling sessions, self-efficacy scores for sexual activity, lifting, and general exertion increased significantly above the treadmill baseline with the greatest proportional increases being observed in the areas of sexual activity and lifting.

The combined effect of treadmill testing and counselling on subsequent physical activity at home was evaluated by comparing the activity logs completed by 18 patients before and after exercise testing and counselling. The highest mean level of physical activity for which these patients expressed 100% confidence before the testing and counselling session corresponded to walking 4 to 5 blocks, running <1 block, climbing 1 to 2 flights of stairs, engaging in sexual intercourse <5 minutes, and lifting <40 pounds (18 kg). Before exercise

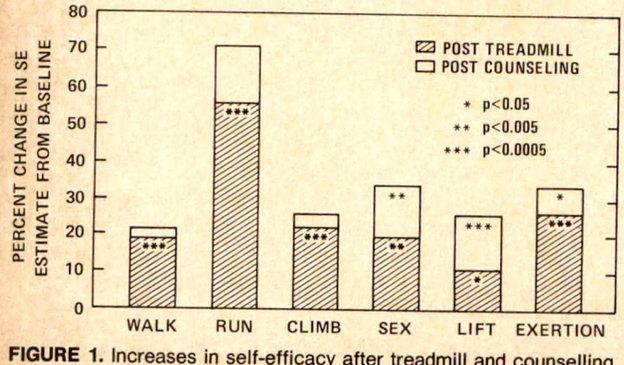

FIGURE 1. Increases in self-efficacy after treadmill and counselling are compared with baseline values obtained before treadmill exercise and before counselling, respectively.

SE_1 \ SE_3	LOW	HIGH
LOW	n = 8 (4) 116 ± 8 BPM 4.6 ± 0.9 METs	n = 12 (1) 136 ± 11 BPM 6.7 ± 1.0 METs
HIGH	n = 5 (3) 123 ± 6 BPM 5.2 ± 1.6 METS	n = 15 (0) 142 ± 12 BPM 6.7 ± 1.1 METs

*Running 1 block

FIGURE 2. Self-efficacy (running 1 block) before (SE_1) and after (SE_3) treadmill exercise and counselling: relation to peak treadmill heart rate (beats/min [BPM]) and work load (mets). Note that 7 of the 8 patients who had treadmill-induced angina pectoris (numbers in parentheses) demonstrated persistently low or decreasing self-efficacy ratings after treadmill testing and counselling (13 patients).

testing and counselling sessions, these patients reported walking an average of 29.1 ± 19.5 minutes a day, attaining a peak heart rate of 78 ± 10 beats/min (Fig. 3). In the week after the testing and counselling, patients reported walking an average of 44.4 ± 27.3 minutes daily, attaining a peak heart rate of 87 ± 14 beats/min. The mean increase in duration of walking and in peak heart rate were both statistically significant ($p < 0.005$).

Self-efficacy as a predictor of subsequent physical activity at home: Changes in self-efficacy scores after exercise testing and counselling predicted subsequent changes in self-reported activity levels. For example, changes in self-efficacy scores for leg work were significantly correlated with self-reported mean heart rate and with average duration of self-reported leg exercise during home activity: $r = 0.53$ and 0.34 (both $p < 0.01$). In contrast, values of peak treadmill heart rate were insignificantly correlated with self-reported mean heart rate and with the average duration of self-reported leg exercise during home activity: $r = 0.30$ and 0.08, respectively.

Discussion

In the present study, self-efficacy judgments proved to be an important link between functional status and physical performance: these judgments predicted how well patients performed on the test and were in turn modified by the test performance. These modified judgments were more accurate predictors of subsequent home activity than was the treadmill performance itself. Findings of the present study have 2 important clinical implications:

1. Patients appear to realistically appraise their capacity to perform various physical activities even before carrying out these activities. For example, the 20 patients who expressed low self-efficacy for running 1 block before treadmill testing demonstrated a lower treadmill heart rate and work load than the 20 patients who expressed high self-efficacy before treadmill testing (Fig. 2). Compared with patients with high self-efficacy scores before treadmill exercise, these 20 patients demonstrated a higher incidence of angina pectoris before infarction and after infarction. Even a subtle degree of angina pectoris, which caused patients no significant distress, appeared to lower their expectations regarding their pending exercise test performance.

2. Patients' judgments regarding their capacity for physical effort become more congruent with their demonstrated exercise capacity after safe completion of treadmill exercise. The relation between self-efficacy and angina pectoris was further strengthened by completion of treadmill exercise: whereas the 20 patients with low self-efficacy before treadmill testing accounted for 5 of 8 patients with treadmill angina, the 13 patients with low or decreasing self-efficacy *after* treadmill exercise accounted for 7 of the 8 patients with treadmill angina. It is not surprising that the strength of association between angina and self-efficacy increased after treadmill exercise, since none of the 40 patients of the study had, before their 3-week test, performed exercise as strenuous as that of treadmill testing. The 13 patients whose self-efficacy scores remained low or decreased after treadmill testing also demonstrated a lower peak treadmill heart rate and work load than the 27 patients whose self-efficacy scores increased from initially low values or remained high. We have previously noted a diminished peak treadmill heart rate and work load in post-MI patients with treadmill-induced angina pectoris.[12]

The close relation noted in our patients between treadmill performance and changes in self-efficacy underscores the importance of such testing as a nonverbal teaching technique, for self-efficacy judgments were made immediately after the test and before the physician and nurse had explained the test results. We cannot exclude the possibility that self-efficacy scores might have increased significantly in patients completing the questionnaires on 3 occasions within a 3-hour period without undergoing exercise testing or counselling. However, significant increases in self-efficacy resulting from repeated administration of the self-efficacy questionnaire have not been noted in previous studies.[8] Self-efficacy theory predicts that direct experience of leg work under safe conditions should preferentially alter self-efficacy for activities similar to the exercise itself, while authoritative persuasion by a physician or nurse should preferentially alter self-efficacy for activities such as lifting and sexual intercourse which are dissimilar to exercise testing. The results of the present study are in keeping with these general principles: performing large muscle dynamic exercise on the treadmill increases self-efficacy for similar tasks such as walking, running, and stair climbing more than for dissimilar tasks such as static effort or sexual intercourse. Further, self-efficacy increased to a greater extent for activities such as jogging, which patients had not yet attempted, than for activity such as walking, which they had already carried out before exercise testing.

Counselling by a physician and nurse exerted the greatest influence on self-efficacy for activities such as lifting and sexual intercourse, which are dissimilar to exercise testing. Self-efficacy for a particular activity was thus shaped by an individual's past success in per-

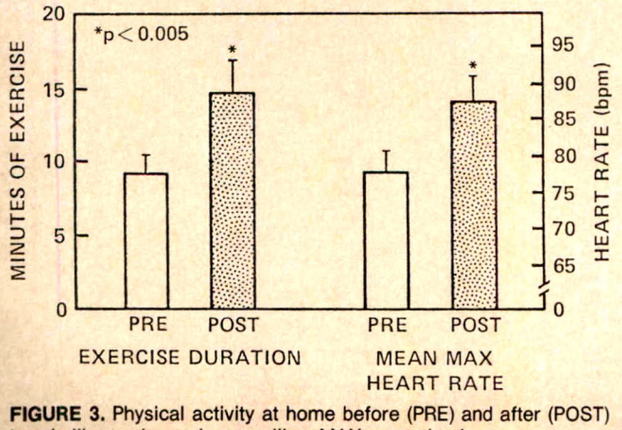

FIGURE 3. Physical activity at home before (PRE) and after (POST) treadmill exercise and counselling. MAX = maximal.

forming that activity or ones similar to it, and by the amount of encouragement given by a respected and credible authority figure.[13] Counselling appears to be an important technique for reinforcing changes in self-efficacy resulting from exercise testing and for generalizing these changes to other physical activities. Physicians should not assume that exercise test performance alone, without counselling with regard to specific activities, will enhance patients' activity levels or speed their resumption of usual physical activities such as return to work.

Exercise testing soon after MI has found wide usage for evaluating prognosis[14,15] and providing individualized guidelines for physical activity.[16] In contrast, the potential of such testing to shape patients' expectations and attitudes regarding their capacity for physical activity has been largely overlooked. The present study suggests that exercise testing and counselling not only influence patients' expectations, but that the expectations themselves mirror the patients' cardiovascular performance. Further, patients' actual performance of physical activity in their home environment was well correlated with their self-efficacy after treadmill testing and counselling. In fact, self-efficacy after treadmill and counselling was superior to peak treadmill heart rate in predicting the duration and intensity of physical activity in the home environment.

Because the present study was designed to examine the relation between perception (self-efficacy) and performance (physical activity in the patient's usual environment), no formal attempt was made to influence patients' physical activity at home. Specifically, in the counselling sessions we did not specify to patients which types of physical activities to be carried out in their usual environment were "appropriate," although for reasons of safety we discouraged any activity during which the "clearance" heart rate would be exceeded. The study was not designed to document the efficacy of physical conditioning commencing soon after MI for enhancing functional capacity. We found in a prior study that patients who had undergone exercise testing soon after MI were relatively active during the next 8 weeks—perhaps as a result of the increased confidence they gained in their capacity for physical effort.[16] The modest but significant increase in the duration of physical activity at home and in the average peak heart rate observed in the present study are in keeping with this prior experience. Further study is required to establish the extent to which the "spontaneous" increases in the duration and intensity of home activity observed in the present study can be augmented by formal exercise conditioning.

A note of caution is appropriate regarding the extrapolation of these results to patients with lower socioeconomic status or greater cardiovascular impairment. The patients of the present study constitute approximately 60% of men aged ≤70 years who are alive 21 days after hospital admission for treatment of MI. The first year mortality rate of these patients undergoing exercise testing is <2%.[17] Approximately two thirds of these patients are classified as white collar and more than 90% of those aged ≤60 years are employed at the time of infarction. Whether the relation between self-efficacy and cardiovascular capacity observed in the present study obtains in older, sicker, and more socially disadvantaged patient populations remains to be demonstrated.

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Treadmill Walking Protocol for the Diagnostic Evaluation And Exercise Programming of Cardiac Patients

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This study (1) describes a treadmill walking protocol which has been used safely in over 40,000 tests since 1960, (2) presents normative data on oxygen consumption ($\dot{V}O_2$) so that it may be determined from work load without direct measurement, and (3) demonstrates simple techniques for early activity prescription or later therapeutic walking programs for patients after myocardial infarction (MI) based on this treadmill test. Normative data are presented on 131 subjects. There were no significant differences in $\dot{V}O_2$ values at the various work loads dependent on age, gender, fitness level, familiarity with the test procedure, clinical status, or the presence or absence of beta blockade. The protocol was then applied in cardiac rehabilitation of 25 patients. As a low level test, in 2 to 9 minutes patients attained 56 to 83% of age-predicted maximal heart rate. The translation of these data into early activity guidelines is shown. For a walking program, the maximal speed attained at 10% grade on the treadmill when walked *on level ground* put patients in the target heart rate zone for cardiovascular conditioning.

Several treadmill exercise test protocols have been described during the past 15 years, each offering special advantages under particular circumstances according to its proponents.[1–4] The Bruce protocol,[6] which has been in use since at least 1964, is probably the most familiar and the most popular because it offers a rapid and safe exercise pattern for which normal standards for blood pressure and heart rate as well as oxygen consumption ($\dot{V}O_2$) have been presented. The Bruce tables for normal or cardiac patients enable the tester to estimate maximal $\dot{V}O_2$ from work load attained or from minutes of treadmill exercise (without direct measurement), and the Bruce nomograms permit derivation of functional aerobic impairment from this information.

However, since the Bruce protocol requires changes in both speed and grade between work loads, it is sometimes difficult for patients to accommodate to the large work increments. At times in deconditioned patients, the peripheral musculature may fatigue before the central circulation can be adequately challenged. It is also more difficult for a lone technician working with a physician to change both speed and grade at just the right time, to take blood pressure, and to collect gases, while making sure the patient is not thrown off balance. In addition, the Bruce test is a walk-jog test with a variable transition point from walking to jogging among subjects.[6] This results in a variety of mechanical efficiencies at stage III (sixth to ninth minute) with varying oxygen costs at this work load so that the Bruce "table" values for $\dot{V}O_2$ may not always hold. Furthermore, during jogging, the electrocardiogram may be distorted by artifacts resulting not only from muscle movement but also from foot impact.

This report (1) evaluates a progressive treadmill *walking* protocol first reported by one of us (AAK) in 1968[7] and used safely in its present form by the authors in over 40,000 tests since 1960; (2) presents normative data on $\dot{V}O_2$ so that it may be determined from work load without direct measurement; and (3) demonstrates simple techniques for activity prescription after myocardial infarction (MI) or therapeutic walking programs based on this treadmill test.

Section I of this report, describing the test itself, is based on the data from 131 subjects who had exercise tests with $\dot{V}O_2$ measurements in the Exercise Laboratory at Montefiore Hospital in New York City during an 8-month period. Section II describes the use of this walking protocol (1) as a low-level test for 12 hospitalized patients recovering from MI, upon which to base activity prescription after discharge, and (2) for direct prescription of a walking program for 13 other patients more than 6 months after myocardial infarction.

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Section I

Patients

Among the 131 individuals included, 117 were men and 14 were women (mean age 52 ± 10 years; range 32 to 69). After the testing procedure the patients were divided into 4 clinical groups as follows. *Group I—Normal:* This group contained 20 persons with no history of coronary artery disease and no risk factors. All were totally asymptomatic and all had negative, nonischemic exercise stress tests. *Group II—Post-MI:* This group consisted of 49 persons, all of whom had recovered more than 3 months earlier from documented acute MI corroborated by electrocardiography or enzyme studies, or both. *Group III—Coronary artery disease without MI:* Among the 17 persons in this group, 4 had significant coronary artery disease verified on angiography by the finding of >70% stenosis (diameter reduction) in >1 coronary artery. The others had ischemic exercise electrocardiograms and thallium scans with an average probability of coronary artery disease of 98 ± 1%.[8] *Group IV—Possible coronary disease:* This group was composed of 45 persons who presented with atypical or nonanginal chest discomfort or pain and who had equivocal, inconclusive, or nonischemic exercise stress test results. They had an average probability of coronary disease of 22 ± 13%.[8]

Methods

Test procedure: All treadmill tests were carried out at least 2 hours after a light meal in an environmental chamber at 19°C and 54% relative humidity. After history taking and cardiologic examination, a 12-lead supine resting electrocardiogram was recorded. Thereafter, the exercise test was performed on a Quinton 18-54 model treadmill. Holding onto the handrail was not permitted. The test protocol is shown in Figure 1. No patient, regardless of size, found it necessary to jog at any stage he or she could carry out. Leads V_5 and aVF were monitored, with 5 to 10 second tracings recorded each minute on a Hewlett-Packard 1500 A electrocardiograph machine. Left-arm cuff blood pressures were measured every minute and phase V (disappearance of sound) was taken as the diastolic blood pressure. Patients reported symptoms every 30 seconds according to a 1+ to 4+ grading system.

Endpoints: Patients exercised to either clinical or physiologic maximal effort. Physiologic maximum (all-out effort) was considered to be the point at which heart rate or blood pressure failed to increase with increasing work loads or where there were other manifestations of insufficient cardiac output and circulatory compromise such as ataxic gait, localized or generalized pallor indicative of cutaneous vasoconstriction, or nausea. Patients were not stopped at any predetermined heart rate. Clinical maximum was taken to be the point of 3+ symptoms. At no time did patients proceed to the 4+ level. Waxing and waning discomfort early in the test was not considered to be 1+ until it became constant although mild.

Although the test endpoints were usually either clinical or physiologic maximum, on occasion patients were stopped before reaching these levels by the testing physician if the diastolic blood pressure was >130 mm Hg, 2 or more premature ventricular complexes appeared in a row on more than 2 occasions, any sustained arrhythmia or bigeminy occurred, there was intermittent or sustained bundle branch block, or extreme generalized fatigue was described.

Interpretation of test results: The stress test was considered ischemic if the tracing demonstrated >1.0 mm horizontal or downsloping S-T segment depression in the majority of complexes in a lead or if there was >2.0 mm of upsloping S-T depression 0.08 second after the J point. Tests were considered "borderline" if there was less S-T depression than this or if the requisite amount of S-T depression was not a consistent finding on all the complexes in 1 lead. Tests were labelled "inconclusive" if the patient was unable to achieve 85% of the predicted maximal heart rate, (Scandinavian-Myrtle Beach tables) or if the electrocardiogram was uninterpretable due to conduction disturbances, ventricular hypertrophy, or medication.

The blood pressure response was considered adaptive if systolic blood pressure rose by 8 to 10 mm Hg/MET. The diastolic response was considered excessive if there was an increase >15 mm Hg or if the pressure, which may initially have been elevated, failed to decrease and remained >100 mm Hg throughout the procedure. All stress test results were read initially by the testing cardiologist and subsequently by an-

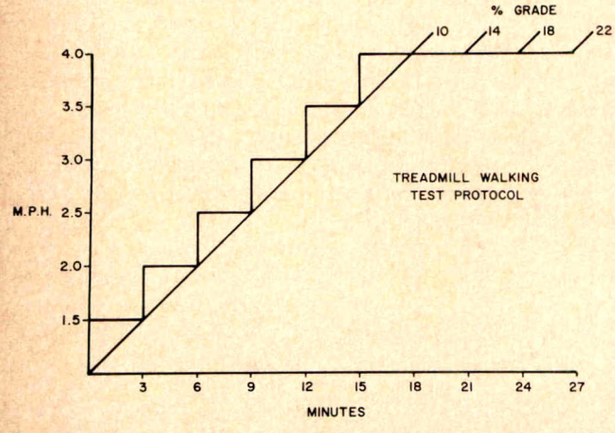

FIGURE 1. Treadmill walking test protocol. M.P.H. = miles per hour, speed of the treadmill (1,609 km = 1 mile); minutes = duration of exercise; % grade = inclination of treadmill.

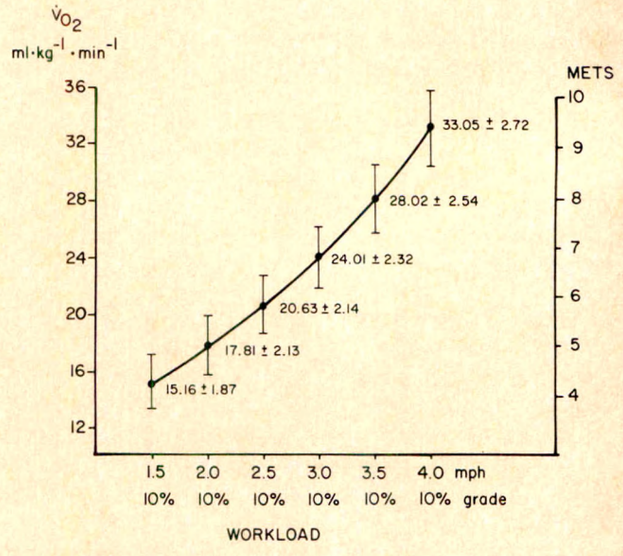

FIGURE 2. Oxygen consumption of the treadmill walking protocol. $\dot{V}O_2$ ml·kg^{-1}·min^{-1} = oxygen consumption expressed as milliliters of oxygen consumed per kilogram of body weight per minute; METS = metabolic unit, that is, oxygen consumption at rest, neither basal nor asleep: 1 MET = approximately 3.5 ml·kg^{-1}·min^{-1}. Values are presented ±1 standard deviation. MET level at 1.5 mph = 4.3; 2.0 mph = 5.1; 2.5 mph = 5.9; 3.0 mph = 6.9; 3.5 mph = 8.0; 4.0 mph = 9.4.

other attending cardiologist who interpreted the tests blindly. A third cardiologist was needed infrequently to adjudicate disagreements.

Respiratory gas measurements: Gas collections were carried out by having the patient breathe through a low resistance Otis-McKerrow valve with expired air channelled through 1.5-inch internal diameter tubing into evacuated Douglas bags. The bags were immediately analyzed for oxygen and carbon dioxide content with a Beckman E-2 oxygen analyzer and a Godart thermal gas analyzer, respectively. Both instruments had been calibrated with gases of known composition which had been verified by repeated micro-Scholander analysis. Expired volume was measured using an American gas meter, previously calibrated against a Tissot spirometer. Minute ventilation, oxygen consumption, and carbon dioxide production (STPD) were calculated.

Statistical Analyses

Values obtained for blood pressure, heart rate, and electrocardiographic wave form for this protocol are not presented in this report. Patients were classified retrospectively into clinical groups as described under Patient Population including these results. Oxygen consumption data were analyzed in depth, however, since maximal $\dot{V}O_2$ provides the best evidence of the functional severity of the impairment among cardiac patients.

Oxygen consumption values at a given work load were included in the analyses only if the following criteria were met: (1) the gas collections were technically completely satisfactory (noseclip tight, no air leaks at the mouth, accurate timing of the collection, analysis carried out immediately, meters functioning accurately and with stability); (2) the patient exercised at a given stage for the full 3 minutes; (3) the $\dot{V}O_2$ for that stage was not the maximal $\dot{V}O_2$; (4) the highest $\dot{V}O_2$ used was collected at least 1 minute before cessation of exercise. By this means, all $\dot{V}O_2$ measurements included were submaximal, and probably "steady state" for the work load.

Oxygen consumption data at the various work loads were compared using analysis of variance (ANOVA) and tests of multiple comparison when necessary (1) among subjects of different ages, (2) among men versus women, (3) for exercisers versus sedentary adults, (4) for those who had previous treadmill tests and those who did not, and (5) among persons receiving, versus those not receiving, beta-blocking drugs.

Thereafter, data were reanalyzed according to the 4 clinical groups described under Patient Population, using the same techniques.

The final compilation pooled data from all subjects to derive $\dot{V}O_2$ values for work load and includes the data for normal subjects and patients aged 30 to 69 years, men and women of varying fitness levels, either receiving or not receiving beta blockade.

Results

Neither morbidity nor mortality resulted from the 131 stress tests. There were no significant differences in $\dot{V}O_2$ values at the various work loads dependent on gender, fitness level, familiarity with the testing procedure, or presence versus absence of beta blockade.

When stratified for work load, age had no significant effect on $\dot{V}O_2$ except for a difference of borderline significance at 4.0 mph/10% grade ($p < 0.05$). At this work load, mean $\dot{V}O_2$ varied at most by 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$.

When examining $\dot{V}O_2$ in the different clinical groups, group differences were suggested only at work loads of 2.0 and 3.0 mph/10% grade (each $p < 0.05$). At 2.0 mph/10% grade, the mean $\dot{V}O_2$ ranged from 16.6 ± 1.5 (Group III) to 18.7 ± 2.4 $ml \cdot kg^{-1} \cdot min^{-1}$ (Group IV). At 3.0 mph/10% grade, results were similar, with a mean $\dot{V}O_2$ of 22.7 ± 1.3 for Group III and 24.8 ± 2.0 for Group IV.

None of these differences between groups exceeded the 10% interindividual variation reported by Wyndham et al[9] for subjects performing walking tasks. Therefore, although of borderline statistical significance, these differences are within the range of individual variation and thus have no clinical relevance. Since these comparisons failed to show meaningful differences according to age, sex, familiarity with the test, medication, or clinical diagnosis between Groups I to IV, data for oxygen consumption were pooled resulting in the normative data shown in Figure 2.

Section II

Use of the Treadmill Walking Protocol in Activity and Exercise Prescription

To evaluate the usefulness of this protocol as the basis for exercise programming, 12 patients had a low-level exercise test at 8 to 23 days after MI and 13 others were evaluated more than 6 months after MI before entering exercise training programs. Characteristics of the patients are listed in Tables I and II.

Procedure: Patients recovering from MI who had a low-level test followed the same protocol as that depicted in Figure 1, beginning at 1.5 mph/10% grade. Exercise was continued until the appearance of 1 to 2+ symptoms, or an arbitrary endpoint at approximately 70% of the age-predicted maximal heart rate. Patients receiving beta blockers followed the same protocol.

The walking test protocol was also carried out in 13 other patients who had sustained MI more than 6 months earlier to either a 3+ clinical or physiologic maximal endpoint. Thereafter, 46 days later (average value) these 13 patients were monitored during *level* treadmill walking, starting at 1.5 mph and increasing 0.5 mph every 3 minutes until the patient achieved 85% of the maximal heart rate attained on the previous stress test. Patients receiving beta blockers had both the walking test and the monitoring on level walking on the same dose of medication. Since exercise incurring a target heart rate of 70 to 85% of maximal attained heart rate is accepted as the appropriate intensity of effort that will result in cardiovascular conditioning, the relation between maximal speed walked on the stress test (at 10% grade) and the heart rate resulting from walking at the same treadmill speed on the flat was examined.

Results: Table I shows that within 2 to 9 minutes the 12 recovering MI patients reached 56 to 83% of their age-predicted maximal heart rates, levels appropriate for a submaximal performance test carried out soon after MI. Eight tests were discontinued by the testing physician at 70% of maximal heart rate and 4 were discontinued because of symptoms. No detrimental effects resulted from any test: 4 demonstrated ischemia by electrocardiogram, 1 was borderline, and the other 7 were negative at these submaximal levels.

TABLE I Use of the Treadmill Walking Protocol as a Low Level Exercise Test

Patient	Days After MI	Age (yr) & Sex	Propranolol (mg/day)	Final Work Load (mph/grade)	Ex Time (min:s)	Heart Rate (beats/min) [% MHR]	Endpoint	Test Result
FG	14	71M	No	1.5/10	2:00	99 [70]	Physician	Neg
MK	18	70M	No	1.5/10	2:30	110 [73]	Fatigue	Neg
SG	17	70M	No	1.5/10	2:40	125 [83]	Physician	Pos
HH	14	62M	No	1.5/10	3:00	110 [70]	Physician	Neg
JC	19	62M	No	2.0/10	6:00	128 [80]	Physician	Bord
SA	23	42F	No	2.0/10	7:30	126 [70]	Physician	Neg
AD	19	49N	No	2.5/10	9:00	123 [71]	Physician	Neg
SG	13	55M	40	1.5/10	3:00	132 [80]	Physician	Pos
FC	12	54F	80	1.5/10	3:00	123 [73]	Physician	Neg
TA	8	50M	400	2.0/10	4:00	96 [56]	Dyspnea	Neg
AC	17	70M	160	2.0/10	6:00	104 [70]	Angina	Pos
BB	17	67M	160	2.0/10	7:30	91 [60]	Angina	Pos

Bord = borderline; Ex time = duration of treadmill exercise; MHR = maximal heart rate; Neg = not ischemic; Physician = test terminated by physician at arbitrary endpoint of 70% predicted maximal heart rate; Pos = positive (ischemic) test; WL = work load.

TABLE II Comparison of Heart Rate on Level Walking and 70 to 85% Maximal Heart Rate During Grade Walking at the Same Speed

Patient	Age (yr) & Sex	Beta Blockers* (mg/day)	Max Speed 10% Grade (mph)	Max HR on EST	THR Range	Level Walk HR
BP	60M	0	2.0	162	113–138	93
LM	63M	0	2.0	126	88–107	102
TL	63M	0	2.5	164	115–139	106
BZ	61M	0	3.0	110	77–94	87
MC	70F	0	3.0	116	81–99	99
TG	44M	0	3.0	150	105–128	95
SF	61M	0	3.0	177	124–150	129
PN	53M	80 prop	1.5	124	88–105	76
HB	57F	120 prop	2.5	134	94–114	96
AM	59M	160 prop	2.5	142	99–121	110
PG	58M	120 prop	3.0	117	82–100	84
LB	44M	40 nad	3.0	126	88–107	83
EL	35M	160 prop	3.5	132	92–112	111

* Patients had the maximal treadmill test and the subsequent monitoring with the same dose of beta blockers.
EST = exercise stress test; HR = heart rate; prop = propranolol; nad = nadolol; THR = target heart rate.

Table II examines the relation between the heart rate attained on level walking and 70 to 85% of the maximal heart rate achieved during grade walking at the same speed in the 13 patients with healed MI. That is, in this table we attempt to determine whether advising the patient to walk on the level ground at the maximal speed attained during treadmill walking at a 10% grade would put him or her in the target heart rate zone for exercise training. Eight of the 13 patients had heart rates within their target range when exercise was prescribed by this method. The other 5 patients were below their target rate. No patient exceeded the target range using this method.

Although the data for the patients receiving beta blockers in both Tables I and II seem essentially the same as the data for those not taking propranolol, too few patients were examined (11 of 25) to make statistical comparisons. These results suggest, however, that this walking protocol is useful both for providing activity guidelines upon hospital discharge after infarction, and for exercise programming later on, regardless of whether the patient is receiving beta blockers.

Discussion

The data presented describe the work load and energy cost of a treadmill walking protocol useful for both diagnostic exercise testing and for activity and exercise prescription for either cardiac patients or normal persons. Measurements were made during treadmill tests done for clinical purposes. Although 20 persons were normal subjects seeking exercise advice, and 45 had a low probability of coronary artery disease, the remaining 66 were coronary heart disease patients. The data are thus representative of office stress testing practice with a prevalence of disease of approximately 50%.

Since the procedure described is entirely a walking test, $\dot{V}O_2$ values follow a smooth curve, rising approximately 1.0 MET/stage from about 4.0 METS at 1.5 mph to 9.0 METS at 4.0 mph at 10% grade. Since there is no transition point between walking and jogging using this protocol, variations in $\dot{V}O_2$ dependent on biomechanical factors were avoided. Astrand (personal communication) has found that at stage III of the Bruce test, oxygen consumption is the same if one runs supported by the handrail or one walks without holding on (Fig. 3). The

OXYGEN UPTAKE $L \cdot min^{-1}$	2.9	2.2	3.2	2.9
HEART RATE Beats $\cdot min^{-1}$	155	138	168	158

Subject's body weight 75 kg

FIGURE 3. Treadmill text (3.4 mph, 14% grade). (Courtesy of Professor Per Olof Astrand, Stockholm, Sweden.)

normative data presented for our treadmill walking test is also essentially the same (within 1 standard deviation) of that which can be derived arithmetically from the formulae and nomograms of Workman and Armstrong.[10,11]

Barnard et al[12] measured the energy cost of this test at higher work loads, that is, when speed remained at 4.0 mph but grade was increased beyond 10% in 4% increments. The MET levels then jumped to approximately 12, 14, and 15 METS at successive stages and $\dot{V}O_2$ values were 43 ± 1 at 14% grade, 50 ± 2 at 18%, and 54 ± 2 $ml \cdot kg^{-1} \cdot min^{-1}$ at 22%, respectively. This test may also be used for fit subjects beginning at 2.0 mph, 10% grade, and progressing to 3.0 mph, 10%, and 4.0 mph, 10%, in 3-minute stages without the intervening work loads, with essentially the same $\dot{V}O_2$ values for work load we have reported, by making use of the figures of Barnard et al.

The $\dot{V}O_2$ values presented here apply only when the person has achieved steady-state conditions (at the end of the stage) and are not precise enough (although clinically usable) for defining maximal performance levels, at which time $\dot{V}O_2$ may no longer be increasing linearly with work load.

Within these guidelines, however, it is appropriate to estimate $\dot{V}O_2$ from the work load reached when patients exercise on the treadmill using this protocol, hence the MET level attainable near-maximally and the MET level at which ischemia becomes evident. Knowledge of MET level at ischemia or near-maximal effort and heart rate at these levels provides the physician with the information needed to prescribe home activity on hospital discharge, rehabilitative conditioning exercise, or an exercise training program.

Use of the Treadmill Walking Test as a Low-Level Test in Early Cardiac Rehabilitation

In our experience, some of the early low-intensity treadmill protocols such as that proposed by Halpenny[13] and expanded by Sivarajan and Bruce,[14] or the graded exercise test protocol of Sheffield,[2] fatigue the patient before an adequate cardiovascular challenge can be presented at 70% of maximal heart rate. Patients are exercising at approximately the 4 MET level only after 9 to 12 minutes of walking according to these protocols, yet some of our patients had to reach the 6 MET level before attaining 70% of maximal heart rate. Extending the duration of the low level protocol beyond 9 to 12 minutes to reach a 6 MET level can sometimes prove exhausting to deconditioned patients. The treadmill walking protocol described here may provide the needed information within 3 to 6 minutes. If the patient is unable to walk at 10% grade for 3 minutes, the test may be stopped and, after a 10-minute rest period, it may be begun again at 1.5 mph, level walking or 5% grade.

Since *maximal* beta blockade may force recovering MI patients to do heavy exercise before reaching 70% of their age-predicted heart rate values, and since beta blockade does not alter oxygen consumption, we limit the low level test to the achievement of approximately

TABLE III Energy Cost (METS) of Various Activities for Convalescent Cardiac Patients*

	Self-Care Activities
1.2	Sitting quietly
1.1–1.5	Standing quietly
1.5–2.0	Eating, conversation
1.5–2.0	Washing hands and face, brushing teeth
1.6–3.4	Washing and dressing, moving about (women)
2.6–4.3	Washing and dressing, moving about (men)
3.7–4.4	Showering
	Diversional Activities
1.5–2.0	Knitting, sewing, listening to radio
1.5–2.0	Playing cards, watching TV
1.8–2.8	Playing a musical instrument—piano, strings
2.8–4.0	Playing organ or drums
2.0–3.0	Light woodworking
	Light Work at Home
1.5–1.9	Office work at a desk, standing, moving about
1.5–2.0	Typing and using office business machines
1.2–3.6	Driving (depends on traffic)
3.1–4.2	Gardening—weeding, using trowel, edging borders, raking
5.3–5.7	Cutting hedges, mowing lawn
	Housework
1.6–2.0	Sweeping floors, preparing vegetables
2.1–3.0	Preparing and serving a meal, washing dishes
2.1–3.0	Dusting, polishing, ironing
3.1–4.1	Bedmaking, vacuuming, shopping (light load)
4.2–5.3	Scrubbing floors, shopping (heavy load)
	Physical Exercise
2.6–2.7	Walking 2.0 mph
3.1–3.2	Walking 2.5 mph
3.6–3.8	Walking 3.0 mph
4.1–4.4	Walking 3.5 mph
2.0–3.4	Light calisthenics (trunk bends, knee raises, arm circles)
2.3–4.4	Bowling
2.0–3.0	Golf with power cart
4.0–7.0	Golf pulling cart
2.5–5.0	Volleyball
4.0–5.0	Table tennis
4.0–5.0	Climbing down stairs
6.0–8.0	Climbing up stairs
4.0–6.0	Sexual activity with familiar partner

* Rest, supine but not basal equals 1.0 MET (metabolic unit). These values are based on average weights of 55 kg (female) and 65 kg (male). All values are approximate since speed of performing activity, proficiency, climatic conditions, and emotional pressure can induce significant variation.

60% of the maximal predicted $\dot{V}O_2$ consumption for age. Sixty to 80% of an individual's maximal $\dot{V}O_2$ is equivalent to 70 to 85% of the maximal heart rate.[15] For persons of average fitness tested using this walking protocol, the 60% $\dot{V}O_2$ level occurs at approximately 2.5 mph/10% grade for those below 50 years of age and at 2.0 mph/10% grade for those over age 50 years. Work load can then serve as the arbitrary termination point for the low-level test done with beta blockers, unless clinical indications dictate to the contrary.

Depending on whether ischemia resulted from the low-level test and whether the physician permits out-of-hospital activities which incur ischemia, the MET level attained on the test is easily equated to cardiac rehabilitation activities (Table III).

Use of the Treadmill Walking Test for Exercise Training Programming

Physical conditioning and exercise training are usually based on a maximal treadmill test carried out at least 6 weeks after MI, although DeBusk et al[16] have begun conditioning patients as early as 3 weeks after MI with the exercise recommendation based on the symptom-limited treadmill test. The appropriate exercise prescription for training involves aerobic exercise (rhythmic, repetitive, continuous) carried out at 70 to 85% of maximal attainable heart rate on the treadmill test for 20 to 30 minutes 3 times weekly, preceded by a warm-up and followed by a cool-down period.[17,18]

Brisk walking can result in a significant training effect on oxygen consumption, blood pressure, and heart rate, as well as favorable changes in body composition (reduction in total weight and percent fat) in 20 weeks.[19] If the individual also carries a 3 to 6 kg (6.6 to 13.2 lb) load in a backpack and walks 30 minutes daily, 5 days weekly at 5 km/h (approximately 3.0 mph), as in the study of Shoenfeld et al[20] in Israel, aerobic capacity can be improved by 15 to 32% in only 3 weeks. Walking offers the advantages of fewer orthopedic problems than jogging, a lower dropout rate (25% versus 40% in most types of training activities), and is slow enough to permit camaraderie and conversation en route.[19]

There have been differences of opinion as to whether treadmill information can be extrapolated to ordinary ambulatory locomotion. By evaluation of the biomechanics involved, Ingen Schenau[21] presented convincing arguments that there is no fundamental mechanical difference between treadmill and fixed surface locomotion; hence our results, although obtained using treadmill training, may be extrapolated to walking outdoors, at least on smooth walking surfaces.

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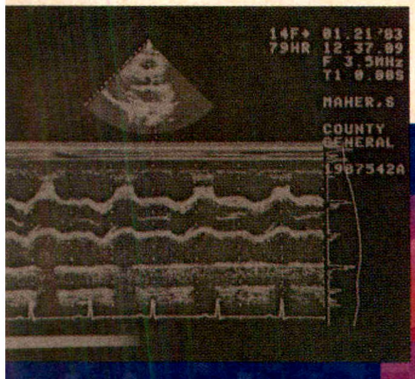

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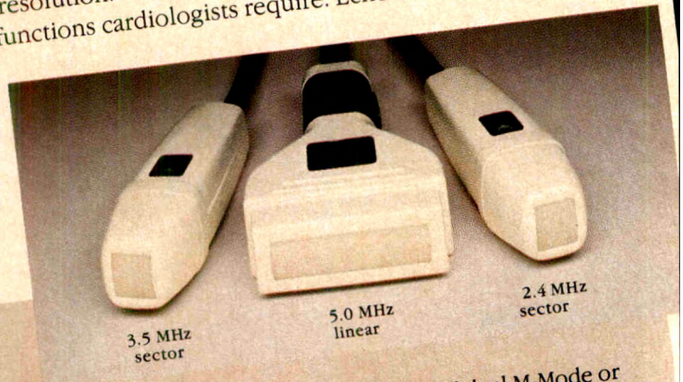

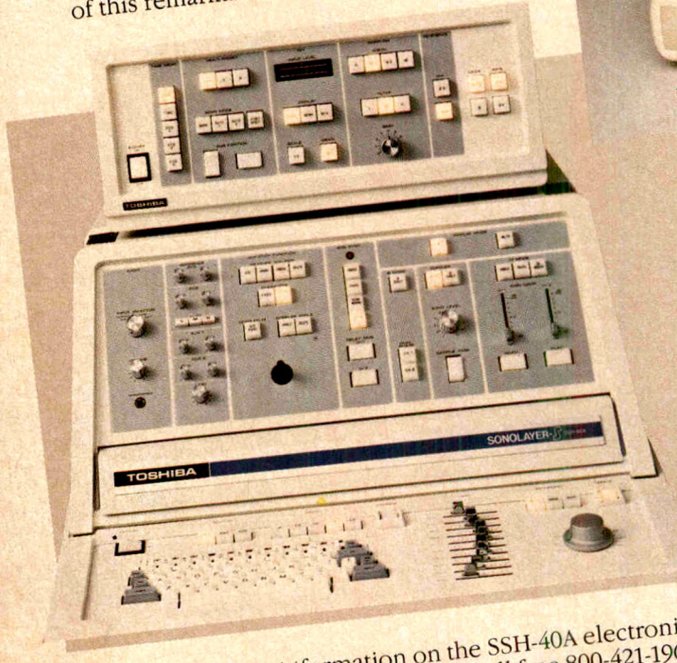

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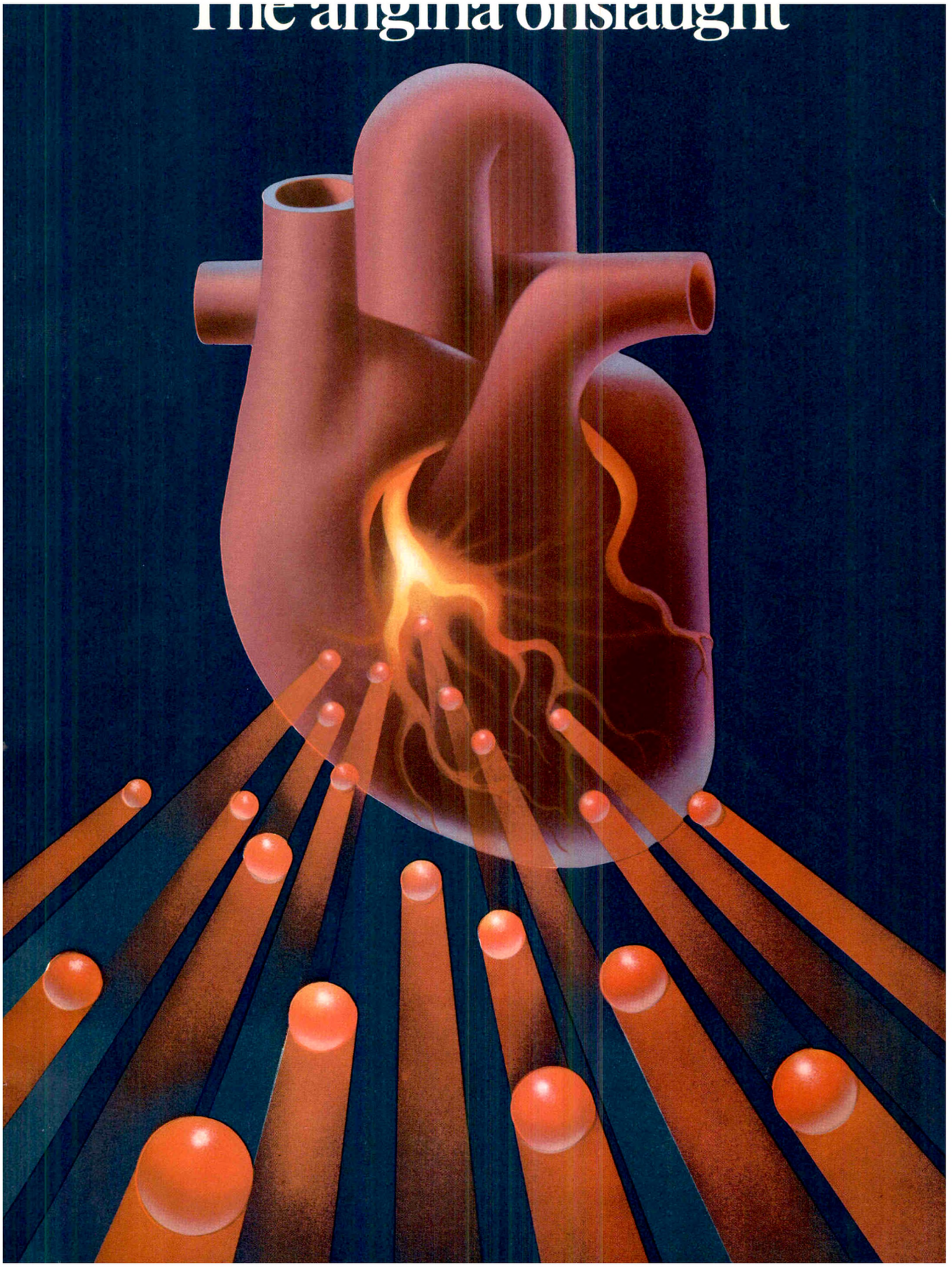

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*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary on next page.

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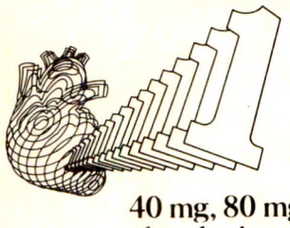

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

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Comparative Functional and Physiologic Status of Active and Dropout Coronary Bypass Patients of a Rehabilitation Program

THAD F. WAITES, MD, EDWARD W. WATT, PhD, and GERALD F. FLETCHER, MD

To assess the benefits of regular participation in a medically supervised cardiac rehabilitation program, 22 patients who had undergone coronary artery bypass (2 groups of 11 each) were studied retrospectively. Group I (mean age 53 years) was currently enrolled in the rehabilitation program. Group II (mean age 56 years) had begun but had discontinued the program. The stated reasons for discontinuation were not medical. There was no difference in entry exercise tests, and presurgical catheterization data in both groups were comparable. Mean peak oxygen consumption (VO_2) by modified Douglas bag technique, heart rate × systolic blood pressure product, and treadmill duration time were recorded in a single testing period. Results revealed that Group I had higher peak VO_2 (30 ml/kg/min) than Group II (24) ($p < 0.005$) and greater treadmill time (11 minutes) than Group II (8) ($p < 0.01$). Nine of 11 subjects in Group I were fully employed, versus 4 of 11 in Group II ($p < 0.01$). One of 11 subjects in Group I had been rehospitalized versus 5 in Group II. None in Group I but 4 of 11 subjects in Group II smoked. Thus, based on the sampling and methodology of this study, it is concluded that coronary artery bypass patients in rehabilitation programs have greater peak VO_2 and treadmill test time, smoke less, are less often rehospitalized, and are more often fully employed than those who are not in such programs.

Coronary artery bypass surgery as an intervention for relief of myocardial ischemia is frequently utilized in the management of patients with coronary artery disease.[1] Although not universally accepted, several studies indicate that bypass surgery improves myocardial function through revascularization.[2,3] After surgery, these patients often enroll in cardiac rehabilitation programs for risk factor modification and exercise training.

It has been demonstrated that such rehabilitation programs improve many indexes of cardiopulmonary function, particularly by increasing oxygen consumption and decreasing both resting and exercise heart rate and systolic blood pressure[4] in patients with coronary artery disease. It has not been demonstrated that surgical intervention coupled with a rehabilitation program is of greater benefit than surgery alone; nor has the value of a structured versus nonstructured rehabilitation program been examined.

For the postbypass patient, does a structured, supervised cardiac rehabilitation program improve cardiopulmonary function more than an individualized, nonsupervised program? Are there other benefits of compliance in a rehabilitation program such as improved return-to-work status and major coronary risk modification?

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These questions were studied by comparing 2 groups of postbypass patients. One group was enrolled in an organized rehabilitation program,[5] and the other group had begun the same program but had voluntarily dropped out.

Methods

Eighteen patients who had undergone coronary bypass were identified in the Atlanta area who had previously been regular participants (now dropouts) of the outpatient cardiac rehabilitation program. A letter explaining the retrospective study was mailed to each. In follow-up phone calls to solicit enrollment, 11 patients agreed to participate. Of those who refused, only 1 cited medical reasons (recent prostate surgery). The other 6 declined for nonmedical reasons (either travel distance or job conflict); none of these were involved in an exercise rehabilitation program elsewhere. A comparable group of 11 postbypass patients who were active in the rehabilitation program was chosen for study. All active patients were at least 9 months postbypass and had been enrolled in the rehabilitation program for at least 6 months with ≥75% attendance. The program consisted of medically supervised and individually prescribed walk or jog, calisthenic, and recreational activities. The subjects participated in these activities 3 times weekly for approximately 1 hour each session (20 to 25 minutes of walk or jog activity). Education in coronary risk factor modification (especially dietary) was an integral part of the program with both individual and group teaching both at the time of exercise testing and in the training program.

Presurgical catheterization data and angiograms of all patients were reviewed. Particular note was made of coronary artery anatomy, left ventricular end-diastolic pressure, regional wall dynamics, and ejection fraction. There was, how-

TABLE I Clinical Features of Active Patients

Patient	Age (yr) & Sex	Surgery to Study Interval (mo)	Extent of Coronary Disease*	Ventricular Function	Ventricular Pressure†	Drugs	Cigarett Smokin
1	52M	14	R, LAD	ASA	Normal	<12	0
2	52M	33	R, LC, LM	None	Akinesia of IP wall	18	0
3	61M	32	LC, D	ASA	Hypokinetic IP wall	<12	0
4	46M	8	R, LAD, LM, LC	HT	Normal	18	0
5	53M	84	LAD	Prop	Normal	<12	0
6	62M	8	R	ASA	I hypokinesia	14	0
7	54M	9	R, LAD, LC	None	AL hypokinesia	12	0
8	41M	20	R, LAD	Prop	IA hypokinesia	18	0
9	71M	36	R, LC, OM	Sulf, Digoxin	Normal	<12	0
10	48M	5	LAD, D	ASA, Chol, Clo	Normal	<12	0
11	58M	24	R, LM	ASA	IA hypokinesia	<12	0

* Number of major vessels with ≥50% diameter reduction.
† Left ventricular end-diastolic pressure (mm Hg).
AL = anterolateral; ASA = aspirin; Chol = cholestyramine; Clo = clofibrate; D = diagonal; HT = hydrochlorothiazide; I = inferior; IA = inferoapical; IP = inferoposterior; LAD = left anterior descending; LC = left circumflex; LM = left main; OM = obtuse marginal; Prop = propranolol; R = right; Sulf = sulfinpyrazone.

TABLE II Clinical Features of Dropout Patients

Patient	Age (yr) & Sex	Surgery to Study Interval (mo)	Extent of Coronary Disease*	Ventricular Function	Ventricular Pressure†	Drugs	Cigarette Smoking
1	48M	24	R, LM	Normal	<12	ASA	0
2	64M	56	R, LM, LC	I Hypokinesia	12	Prop	0
3	61F	57	R, LM	Normal	<12	HT, Prop	+
4	47M	53	LAD, LC	Normal	<12	None	+
5	63M	36	R, LAD, LC	I Akinesia	30	Digoxin, Prop, HT	0
6	53F	33	LAD	Normal	<12	ASA, Prop	+
7	51F	14	R, LAD, LC	Normal	13	Prop	+
8	55M	12	R, LAD, OM	Akinetic apex	14	Digoxin	0
9	59M	32	LAD, LM, LC	Aneurysm	<12	None	0
10	58M	69	R, LAD, LC	AL hypokinesia	<12	None	0
11	55M	9	R	Normal	<12	Digoxin, Sulf	0

* Number of major vessels with ≥50% diameter reduction.
† Left ventricular end-diastolic pressure (mm Hg).
AL = anterolateral; ASA = aspirin; Chol = cholestyramine; Clo = clofibrate; D = diagonal; HT = hydrochlorothiazide; IA = inferoapical; IP = inferoposterior; LAD = left anterior descending; LC = left circumflex; LM = left main; OM = obtuse marginal; Prop = propranolol; R = right; Sulf = sulfinpyrazone.

ever, no data on the presurgical exercise capacity (baseline peak oxygen consumption) of the 2 groups. Postsurgical exercise tests performed at least 3 months postoperatively for entry into the rehabilitation program were reviewed and compared, and were found comparable with regard to test duration, arrhythmias, electrocardiographic changes, heart rate, and blood pressure response.

All subjects were then scheduled for treadmill exercise testing to be done with both physiologic and hemodynamic studies. The testing procedure was explained and use of the modified Douglas bag technique was demonstrated. Testing was performed by standard protocol.[6] Precisely at the peak of exercise, a single breath sample of expired air was collected for calculation of instantaneous peak oxygen consumption.[7] (Single breath method is felt to be comparable to the Max Planck technique which correlates well with the Douglas bag technique.[8]) After a rest period, the purpose of the study was discussed further and a questionnaire was presented verbally. Exercise testing results were interpreted independently by 2 physicians. Rate-pressure product was calculated from peak heart rate in beats per minute and peak systolic blood pressure in millimeters of mercury. Standard equations[7] were used to calculate peak oxygen consumption from the expired air sample. Gas was analyzed by Beckman automatic gas analyzer (OM-11 for oxygen and LB-2 for carbon dioxide). Standard reference calibrations were performed before and after each measurement using known reference gases.

Data were analyzed by paired and nonpaired t test using 2-way tables (1 degree of freedom) and standard chi-square equations.

Results

Clinical features and physiologic and functional data acquired in the trained state for active subjects and at the same time (6-month study period) for the dropouts are seen in Tables I to V.

There was no difference in age between the active and the dropout groups (active mean = 54 years, dropout mean = 56 years); however, the age of Patient 9 in the active group (71 years) may have influenced this data to a degree, especially with the small group numbers. Body weights and heights were comparable (active mean = 80.9 kg, dropout mean = 80.6 kg and active mean = 177.2 cm, dropout mean = 176.9 cm, respectively). All active patients were male, while 3 of the dropouts were female. Peak oxygen consumption in ml/kg/min was significantly different (active mean = 30 versus inactive mean = 24) ($p < 0.005$), as well as

TABLE III Exercise Testing Data in Active Patients

Patient	VO_2	Mets	Time on Treadmill (min)	Peak Heart Rate (beats/min)	Peak Blood Pressure (mm Hg)	Rate-Pressure Product	Treadmill Results in S-T Displacement (mV)	Weight (kg)	Height (cm)
1	25.7	7.3	9	145	145/50	21,025	0	87.3	182.9
2	27.8	7.9	10	155	136/72	21,080	0	86.4	179.9
3	30.3	8.6	9	150	190/74	28,500	0	86.4	172.3
4	28.4	8.1	12	160	185/80	29,600	0	80.9	177.8
5	40.8	11.6	14	130	160/75	20,800	0	78.6	179.9
6	35.3	10.1	13	150	172/74	25,800	0	60.9	167.6
7	29.1	8.3	12	165	160/40	26,400	0	84.1	176.8
8	28.6	8.3	12	140	158/60	22,120	0	85.0	180.3
9	30.2	8.6	5	145	180/90	26,100	0	88.2	179.4
10	36.3	10.4	12	160	160/70	25,600	±	78.2	180.3
11	22.8	6.5	8	118	150/74	11,700	0	74.5	171.6
Mean values	30.5	8.7	11	147	163/69	23,520	. . .	80.9	177.2

Met = metabolic equivalent (1 met = 3.5 ml/kg/min of oxygen consumption); VO_2 = peak oxygen consumption in ml/kg/min.

TABLE IV Exercise Testing Data in Dropout Patients

Patient	VO_2	Mets	Time on Treadmill (mins)	Peak Heart Rate (beats/min)	Peak Blood Pressure (mm Hg)	Rate-Pressure Product	Treadmill Results in S-T Displacement (mV)*	Weight (kg)	Height (cm)
1	35.1	10.02	14	180	160/60	28,800	0	85.9	190.5
2	17.9	5.1	7	120	160/70	19,200	0.2	97.3	180.0
3	17.7	5.1	6	135	160/90	21,600	0	69.1	161.3
4	23.5	6.7	7	155	180/40	27,900	0	88.2	180.3
5	21.9	6.3	7	100	180/70	18,000	0	86.4	177.4
6	22.5	6.4	8	108	180/90	19,440	0	83.2	181.6
7	19.5	5.6	9	125	170/70	21,250	0	63.6	166.3
8	26.1	7.5	9	155	180/90	27,900	0	87.7	180.3
9	29.1	8.3	10	160	140/80	22,400	0	76.6	174.8
10	20.2	5.9	7	150	200/80	30,000	0.2	69.5	176.8
11	27.8	7.9	10	154	200/70	33,880	±	79.1	177.4
Mean values	23.7	6.8	9	140	175/74	24,579	. . .	80.6	176.9

* Millivolts in horizontal negative displacement.
Met = metabolic equivalent (one met = 3.5 ml/kg/min of oxygen consumption); VO_2 = peak oxygen consumption in ml/kg/min.

treadmill time (active mean = 11 minutes, inactive mean = 8 minutes) ($p < 0.001$). Peak rate-pressure products, however, were not significantly different between the groups.

Nine of 11 active patients had returned to full working status compared with only 4 of 11 dropouts ($p < 0.01$). Only 1 active patient has been hospitalized (on 2 different occasions); however, 5 of 11 dropouts have been rehospitalized for a total number of 7 rehospitalizations. All of the rehospitalizations were because of patient symptoms or circumstances and none were solely at the request of the medical-surgical team. None of the active but 4 of 11 dropout patients continued to smoke. The period of time for follow-up from start of the program was comparable between groups.

Discussion

Peak oxygen consumption correlates well with cardiovascular conditioning[9,10] and is an index of maximal cardiovascular and pulmonary function.[11] An increase in the level of habitual physical activity will increase peak oxygen consumption and revascularization resulting from bypass surgery will also increase peak oxygen consumption.[3] It has not previously been shown that bypass surgery plus an organized program of ex-

TABLE V Functional Features of Patient Population

Patients	Work Status	Hospital Admissions Since Surgery
	Actives	
1	Full time	None
2	Full time	None
3	Full time	None
4	Full time	None
5	Full time	2—for recath-patent grafts
6	Full time	None
7	Full time	None
8	Full time	None
9	Not working (retired before).	None
10	Full time	None
11	Not working	None
	Dropouts	
1	Full time	None
2	Not working	1—for recath-patent grafts
3	Not working	2—1 for recath-patent grafts
4	Not working	2—1 for recath-patent grafts
5	Not working	1—for recath-patent grafts
6	Not working	1—for recath-patent grafts
7	Not working	1—for recath-patent grafts
8	Full time	None
9	Not working	None
10	Full time	None
11	Full time	None

Recath = repeat coronary arteriography.

ercise improves results over bypass surgery alone; however, in this study, the active patients attained a higher mean peak oxygen consumption than those in the dropout group.

Symptom limited endpoint time on an exercise test is an indirect measurement of myocardial oxygen consumption and is an indication of myocardial blood flow.[12] Coronary bypass surgery improves myocardial blood flow and thus increases exercise test duration.[13] Previous data have shown that bypass patients further improve their time on treadmill testing after participation in an exercise program. These data also revealed improvement in treadmill duration time for bypass patients who were not regularly exercising.[14] In our study, however, the active postbypass patients were capable of a greater duration on the treadmill test than the dropouts.

The difference in oxygen consumption between our groups likely reflects a "general" training effect with larger stroke volume and cardiac output. Though the dropouts had higher peak blood pressures with testing, there was no significant difference in peak rate-pressure product between the 2 groups. Of note, 3 active and 6 dropout patients were receiving propranolol. When the work load is the same, exercise with propranolol results in lower heart rate, blood pressure, and myocardial oxygen consumption than exercise without it.[15] This greater number of patients on propranolol in the dropout (6) versus the active (3) group may therefore have accounted for some differences between groups.

General state of well-being is difficult to assess. However, based on personal interview, it seems that the active patients "felt better" than the dropouts because they were enjoying the program and the "comradeship" with other patients and staff. Of note, 4 of the 11 dropouts (Patients 2, 4, 6, and 8) (Table II) later rejoined the exercise program. Two of these 4 (Patients 4 and 6, Table II) were smokers.

Functional features of the patients are seen in Table V. None of the active patients smoked cigarettes compared with 4 of the dropouts who continued to smoke. Eight of each group had previously smoked. Peer pressure is likely a factor in this difference and the motivation to remain in a tri-weekly rehabilitation program probably also motivates them to stop cigarettes. Nine of the 11 active patients were still working. One received disability retirement before surgery; the other (age 71 years) retired at age 65. Only 4 of 11 dropouts were working. Two had physical disability retirement before surgery. The other 5 listed various health reasons (prostatism in 2, low back pain in 2, and peripheral vascular disease in 1); however, none in either group listed angina pectoris as a reason for not working. As noted, only 1 of the active versus 5 of the inactive patients were rehospitalized. All hospitalizations for the dropouts occurred 6 or more months after withdrawing from the program. In each instance the reason for rehospitalization was to have repeat coronary arteriograms because of symptoms to evaluate status of the bypass grafts. Results of studies revealed patent grafts in all subjects (Table V).

The active patients, therefore, seemed to benefit from the rehabilitation program; it is felt that compliance with the program was a significant factor. When comparing the 2 groups by presurgical data, both had comparable numbers of significantly diseased coronary arteries, left ventricular wall contraction, and end-diastolic pressure. According to operative notes, revascularization was considered complete in all cases. Postsurgical preexercise data was evaluated by comparing entry treadmill tests for the rehabilitation program. These postsurgical treadmill test results were comparable in that there was no difference between the groups with respect to duration time, electrocardiographic changes, arrhythmias, systolic blood pressure increase, or attained heart rate. There, it was felt that the groups were comparable in degree of underlying cardiovascular disease.

All patients were medically stable and motivated to begin the rehabilitation program. Though it is possible that the reason for dropping out was physical or medical inability to continue, none of the dropouts stated such reasons. In addition, there seemed to be no difference in response to the educational program between active and dropout patients. Although most had conflicts of time or distance given as reasons for dropping out, the true reasons are not clear and are likely multifactorial.

Based on the results herein discussed, coronary bypass patients in a medically supervised program have greater oxygen consumption and exercise test duration, are more often at full working status, have fewer hospital readmissions, and are less likely to smoke. These data support benefits of patient compliance in an organized cardiac rehabilitation exercise program; however, some of these beneficial effects are likely due to strong selection factors associated with entrance into and adherance to the highly structured program.

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Exercise Versus Cold Temperature Stimulation During Radionuclide Cineangiography: Diagnostic Accuracy in Coronary Artery Disease

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To assess the relative efficacy of cold temperature stimulation and bicycle exercise in inducing ischemia detectable by radionuclide cineangiography, we used both stresses to study 20 normal subjects and 54 patients with coronary artery disease (CAD), 42 of whom had not had myocardial infarction. Cold stimulation caused increases in heart rate and arterial pressure which were significantly less marked than those caused by exercise. Regional left ventricular dysfunction was induced by cold in 24 of 41 patients without previous infarction (57%) and by exercise in 34 of 42 patients (81%) ($p < 0.05$), but was absent in all normal subjects during either stress. Left ventricular ejection fraction increased during exercise in all normal subjects (average increase 18%) but decreased during cold stimulation in 12 of 20 subjects. Because of the disparate response of normal subjects to the 2 stresses, the sensitivity and specificity of radionuclide cineangiography were assessed over a wide range of ejection fraction changes independently for each stress. During exercise, at ejection fraction changes in which specificity was high, sensitivity also was high, but during cold stress, specificity was relatively poor at ejection fraction changes in which sensitivity was high, and sensitivity was relatively poor when specificity was high. During exercise, patients with anatomically severe (3-vessel, left main, proximal left anterior descending) disease manifested significantly greater reduction in ejection fraction than did patients with less severe stenoses (−10% versus −3%, $p < 0.001$); cold stimulation did not lead to similar separation (−2% versus −3%, difference was not significant). Therefore, when radionuclide cineangiography is performed, exercise is more effective than cold stress in separating normal subjects from patients with fixed obstructive CAD and in identifying patients with anatomically severe CAD.

The detection of regional and global left ventricular dysfunction induced by stress can be achieved noninvasively by the use of radionuclide cineangiography.[1–3] As a result, when employed in association with exercise, radionuclide cineangiography has proved to be a highly accurate means of diagnosis of coronary artery disease (CAD).[3] However, the sensitivity of radionuclide cineangiography during exercise in detecting CAD ranges between 82 and 98%, indicating that some cases may not be detected.[3–10] In addition, because of other physical infirmities, exercise cannot be performed by all individuals suspected of having CAD. Therefore, an alternative means of stress might be desirable if it could produce myocardial ischemia detectable by radionuclide cineangiography. Cutaneous cold stimulation has been reliable in producing evidence of myocardial ischemia.[11–14] Moreover, the method is applicable in patients who cannot perform standard exercise procedures. Therefore, in conjunction with radionuclide cineangiography, cold stimulation may be a potentially useful alternative to exercise in the detection of patients with CAD. In addition, experimental evidence suggests that results of cold stimulation may serve to complement results obtained during exercise. Ischemic heart disease

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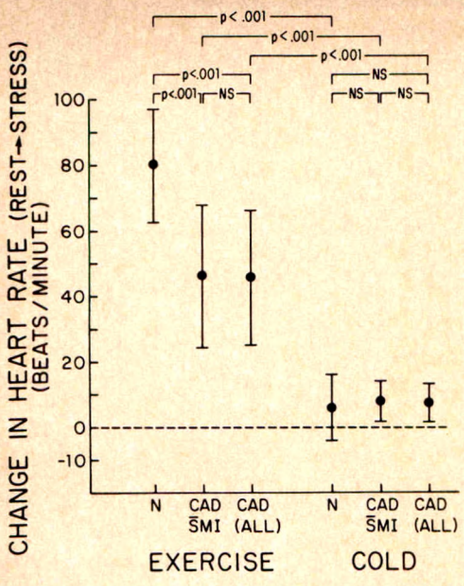

FIGURE 1. Heart rate response to exercise and cold stress. CAD (ALL) = all patients with coronary artery disease; CAD S̄MI = patients with coronary artery disease without previous infarction; N = normal subjects; NS = not significant.

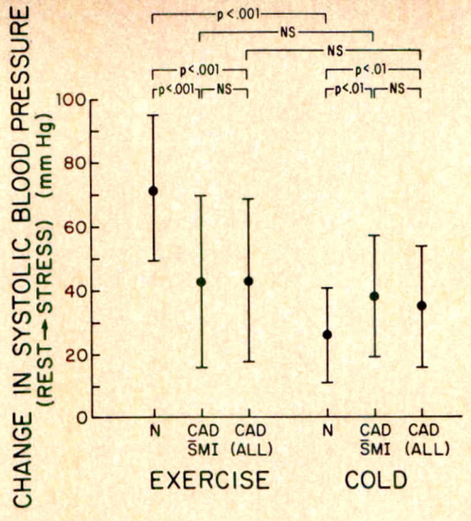

FIGURE 2. Systolic blood pressure response to exercise and cold stress. Abbreviations as in Figure 1.

currently is viewed as the result of coronary artery obstruction comprising both fixed and dynamic components in varying proportions. Acceptance of this concept implies the potential inadequacy of exercise as an ischemic stress, particularly when the goal of evaluation is the quantification of the effects of CAD, because exercise may not reproducibly stimulate the dynamic component of coronary artery obstruction. In contrast, cold stimulation may induce coronary artery spasm at sites of atheromatous plaques,[15] thus decreasing myocardial oxygen supply, while simultaneously causing peripheral vasoconstriction which, like exercise, increases myocardial oxygen demand. Therefore, the present investigation was undertaken to assess the diagnostic efficacy of cold stimulation during radionuclide cineangiography and to compare the accuracy of this approach with that obtained when standard exercise testing is employed with radionuclide cineangiography or with electrocardiography. In addition, the relation between the intensity of cold-induced left ventricular dysfunction and the extent of anatomic obstruction of the coronary arteries was evaluated.

Methods

Studies were performed in 49 men and 5 women aged 33 to 79 years who presented at New York Hospital for evaluation of known or suspected CAD. Fixed obstructive CAD (≥50% reduction in luminal diameter of at least 1 major coronary artery with the extent of luminal diameter reduction determined by trained senior physician observers from films obtained at catheterization) was documented in 49 patients at coronary arteriography, and by a history of documented myocardial infarction in an additional 5 patients. In total, 12 of the 54 patients had documented evidence of previous myocardial infarction at the time of study. Nitrate therapy was stopped at least 6 hours before the studies and propranolol was stopped at least 24 hours before testing. Patients were excluded from the study if valvular or cardiomyopathic abnormalities were apparent by clinical assessment, echocardiography, or cardiac catheterization. All patients were in normal sinus rhythm before and during testing.

In addition, 20 normal subjects aged 23 to 51 years without clinical, echocardiographic, or exercise electrocardiographic evidence of heart disease, and thus with a very low pre-test likelihood of disease, were studied. Normal subjects were volunteers, not patients, from the local community, recruited specifically for study of radionuclide cineangiographic responses and, therefore, were not taking cardioactive medications of any kind.

In each patient or normal subject, radionuclide cineangiography was performed at rest, during exercise, and during cold stimulation using the standard electrocardiogram-gated equilibrium technique previously described in our laboratories.[1,2] During rest and during cold stimulation, studies were acquired in both the 35° right anterior oblique and modified left anterior oblique (15° caudad angulation, visually determined right and left ventricular separation) positions. In 24 patients, right anterior oblique views were not obtained during cold stimulation because of patient refusal to undergo a second cold stress. During exercise, studies were acquired only in the modified left anterior oblique position. In vivo red cell labeling was performed as previously described, using standard methods.[16]

Studies were performed at rest before studies during either stress. After the initial stress study, a 20-minute recovery period was permitted before the second series of studies at rest and during stress was performed. Order of testing was alternated both in normal subjects and in patients with presumed coronary artery abnormalities according to the order of appearance of patients in the laboratory; order of appearance was determined by clerical personnel unaware of the existence or nature of the study.

Exercise stress involved supine bicycle ergometry, beginning at a load of 25 W and increased by 25-W increments every 2 minutes, as previously described.[1,2] Heart rate was monitored every minute and blood pressure every 2 minutes during exercise. Exercise was continued until the development of limiting angina, dyspnea, or fatigue. Imaging was undertaken during maximal exercise, always involving at least the final

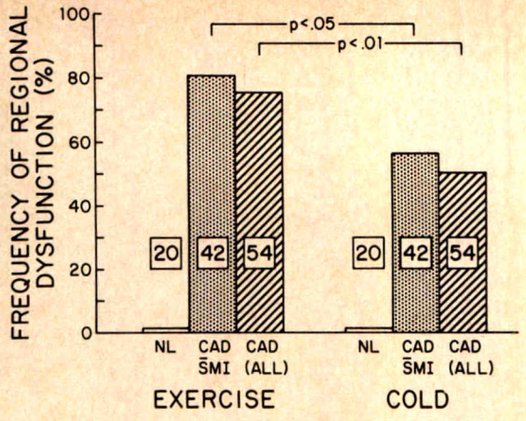

FIGURE 3. Frequency of new regional dysfunction seen with exercise and cold stress during radionuclide cineangiography (RNCA). Numbers in boxes denote population sizes. NL = normal; other abbreviations as in Figure 1.

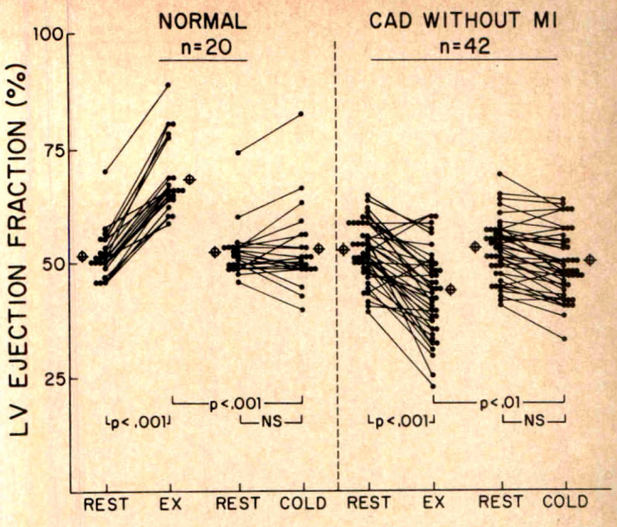

FIGURE 4. Left ventricular ejection fraction response to stress in normal subjects and in patients with coronary artery disease without previous myocardial infarction (MI). CAD = coronary artery disease; EX = exercise; LV = left ventricular.

1.5 minutes of exercise. Cold pressor testing was performed by immersion of the subject's right hand up to the wrist in a bucket of ice water at 4°C. Heart rate was monitored every 30 seconds and blood pressure every minute. After 1 minute of cold exposure, imaging in the left anterior oblique position was undertaken for 2 minutes; the total ice immersion time was 3 minutes. After a 5-minute rest period, the foregoing sequence was repeated with imaging in the right anterior oblique position.

During exercise and in the 3 minutes immediately after exercise, the electrocardiogram was continually monitored with a V_5 lead to monitor anterior vector variations and a modified aVF lead to monitor inferior vector variations. Electrocardiographic recordings were obtained at rest, during maximal exercise, and, if additional abnormalities were noted on the monitoring oscilloscope, during the postexercise period. Electrocardiographic S-T segment variations during exercise were considered indicative of CAD if net S-T segment depression 0.08 seconds after the J point was ≥0.1 mV as compared with the tracing obtained at rest, and the S-T segment slope was 0 or negative.

Radionuclide cineangiograms were assessed visually for evidence of regional dysfunction by observers blinded to the intervention employed and to the clinical and angiographic status of the patient. Studies from normal volunteers and from patients were assessed separately. Regional function assessment is based on the visual recognition of abnormalities in the movement of regional blood volumes.[1–4,9] In this study, a diagnostic regional abnormality was considered present if it was noted in the stress study but was not present in the resting study. Left ventricular ejection fractions were assessed by the count-based method previously described.[17–19] Statistical assessments were performed with the Student's *t* test, analysis of variance, and the chi-square test.

Results

Heart rate and systemic arterial pressure responses to exercise and cold stimulation in each group are depicted in Figures 1 and 2. Heart rate increased significantly ($p < 0.001$) in all groups during exercise, although normal subjects achieved a significantly ($p < 0.001$) higher heart rate than did all other groups. Heart rate tended to increase during cold stimulation in normal subjects; although on the average the heart rate increased to the same degree in patients with CAD, the latter changes achieved statistical significance ($p < 0.01$).

Systemic arterial pressure increased significantly ($p < 0.001$) in all groups during both exercise and cold stimulation. Higher systolic arterial pressures were seen during exercise in normal subjects than in patients with CAD ($p < 0.001$). In contrast, during cold stimulation, patients with CAD had significantly ($p < 0.01$) higher systolic pressure than did normal subjects. However, systolic pressure response was not significantly different in patients with CAD when results during exercise were compared with those obtained during cold stress. The double product (heart rate × systolic arterial pressure) was significantly greater for all subjects during exercise (23,606 ± 7,125) than during cold stimulation (12,841 ± 3,513, $p < 0.001$).

The incidence of regional dysfunction noted during exercise and during cold stimulation is shown in Figure 3. Regional dysfunction was not seen in normal subjects at rest or during either form of stress. Exercise resulted in regional dysfunction in 34 of 42 (81%) patients with fixed obstructive CAD without previous infarction and in 41 of 54 (76%) of all patients with fixed obstructive CAD, significantly higher frequencies of dysfunction than those produced by cold stimulation (57%, $p < 0.05$, in patients without previous infarction, and 50% in all patients, $p < 0.01$). Thus, when regional dysfunction induced during stress is employed as the indicator of CAD, radionuclide cineangiography is more sensitive when exercise, rather than cold stimulation, is employed. The specificity of the test is equivalent (100% in this series) when either form of stress is employed.

Individual responses of left ventricular ejection fraction during exercise are depicted in Figure 4. During exercise, all normal subjects manifested an increase in left ventricular ejection fraction as compared with the

value obtained at rest; the average increase was 18% ($p < 0.001$ compared with the resting value). Among the 42 patients with fixed obstructive CAD without previous infarction, the ejection fraction decreased during exercise in 36 patients (86%). Among all 54 patients with fixed obstructive CAD with and without previous infarction, the ejection fraction decreased during exercise in 44 patients (81%). Of the patients with fixed obstructive CAD who had an increased ejection fraction during exercise, the increase was <5% in 4 patients; previous studies suggest that normal subjects almost invariably have an increase in ejection fraction ≥5% during exercise,[3] a finding corroborated in the normal population in the present study. Using the absence of an increase in ejection fraction of ≥5% from rest to exercise as the criterion for a positive test, the sensitivity of radionuclide cineangiography in detecting patients with CAD was 90% in patients without previous infarction and 91% in all patients with CAD.

Individual ejection fraction responses to cold stimulation are shown in Figure 4. In each patient, the ejection fraction at rest before cold stimulation varied little if at all from the baseline before exercise, and the average ejection fraction for each group was indistinguishable when the 2 resting values were compared. During cold stress, ejection fraction increased in 8 of 20 normal subjects, decreased in 10, and remained unchanged in 2 when compared with resting values. The maximum diminution in ejection fraction was 7%, and only 2 of 20 normal subjects manifested a decrease >5% with cold stress. In patients with CAD without previous infarction, ejection fraction varied widely during cold stimulation, although the average change for the group from rest to cold stress was small (average change −3%, not significant [NS] versus the value at rest). Of the 42 patients without previous infarction, 33 (79%) manifested a decrease during cold stress, but only 11 of 42 (26%) manifested a decrease >5%, the decrement attained by 2 of 20 (10%, NS) normal subjects. Among all 54 patients with CAD, average ejection fraction change during cold stimulation also was small (average change −3%, NS versus value at rest). Forty-two of these 54 (78%) patients manifested a decrease in ejection fraction and in 15 of 54 (28%) the decrease was >5%.

In comparing the efficacy of exercise stress and cold stress in facilitating detection of patients with fixed obstructive CAD from radionuclide cineangiograms, assessment of relative sensitivity and specificity based on changes in ejection fraction is difficult, because of the differences in ejection fraction response of normal subjects to the 2 different stresses. Therefore, to determine which of the 2 stresses permitted the better separation of normal subjects from patients with fixed obstructive CAD when diagnostic criteria were based on ejection fraction changes, the relation between sensitivity and specificity of radionuclide cineangiography for each of a large series of ejection fraction changes was determined for each of the 2 stresses (Fig. 5). As is apparent from Figure 5, over a wide range of ejection fraction changes, sensitivity of radionuclide cineangiography during exercise varied to a moderate extent but throughout this range the test maintained a high specificity. In contrast, during cold stimulation over the same range of ejection fraction changes, when sensitivity was relatively high, specificity was relatively low, and when specificity was high, sensitivity was relatively low. Sensitivity and specificity were equally high when the diagnostic criterion was an ejection fraction change of −1%; at this level, sensitivity and specificity each were 67%, significantly ($p < 0.01$) less than the maximal sensitivity and specificity achievable at a given ejection fraction change with exercise stress (sensitivity 98%, specificity 100% at ejection fraction change of +8%). Thus, over a wide range of stress-induced ejection fraction changes used as the criteria for diagnosis of

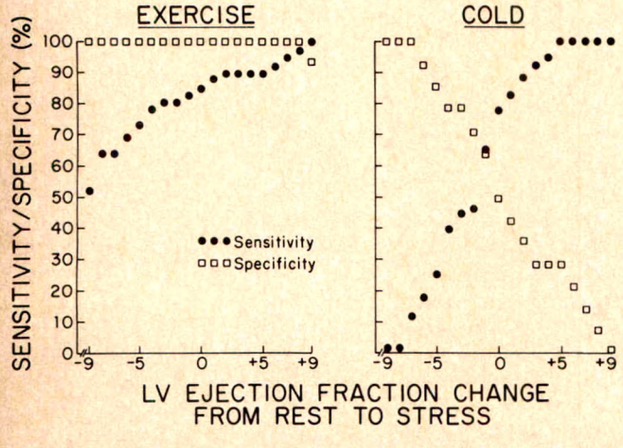

FIGURE 5. Sensitivity and specificity of radionuclide cineangiography in detecting coronary artery disease based on the change in left ventricular ejection fraction from rest to stress in patients with coronary artery disease without previous myocardial infarction. LV = left ventricular.

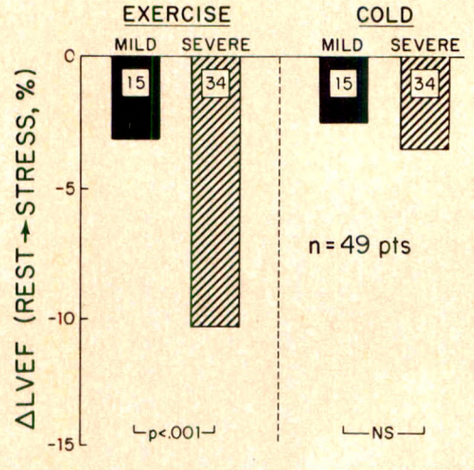

FIGURE 6. Change in left ventricular ejection fraction (ΔLVEF) from rest to stress in relation to anatomic severity of coronary artery disease. MILD = ≥50% luminal diameter obstruction of 1 or 2 major coronary arteries, excluding ≥90% occlusion of proximal left anterior descending coronary artery; SEVERE = ≥50% luminal diameter obstruction of all 3 major coronary arteries or of left main coronary artery, or ≥90% occlusion of proximal left anterior descending coronary artery.

TABLE I Relation of Anatomic and Functional Severity of Coronary Artery Disease

Major Arteries With ≥50% Luminal Diameter Stenosis	n	Mean Ejection Fraction Change From Rest to Stress: Exercise	Cold	p
Single (without proximal LAD)	4	−1.50	−4.75	NS
Double (without proximal LAD)	11	−3.55	−1.55	NS
Triple (without proximal LAD)	13	−8.69	−2.77	<0.02
Proximal LAD (≥90%)	13	−11.31	−3.23	<0.01
Left main	8	−11.38	−4.88	<0.05

* p <0.03.
LAD = left anterior descending; NS = not significant.

fixed obstructive CAD, either sensitivity or specificity, or both, were significantly (p <0.05) lower when cold stress rather than exercise stress was employed.

In comparison with the results of radionuclide cineangiography, sensitivity of exercise electrocardiography (64%; 25 positive results of 39 assessable electrocardiograms) was equivalent to that achieved during cold stimulation (56%, NS) and less than that noted during exercise, although not significantly so (80%, NS), when regional dysfunction was employed as the criterion for the diagnosis of fixed obstructive CAD. Because the presence of exercise electrocardiographic abnormalities was used to exclude subjects from our normal group, no determination of relative specificity could be made and, similarly, no comparison based on ejection fraction criteria could be undertaken.

Comparison between the responses in ejection fraction induced by exercise and by cold indicate that the magnitude of changes produced by exercise generally was more closely related to the severity of anatomic obstructions in the coronary arteries than were changes induced by cold (Fig. 6, Table I). Thus, for example, patients with ≥90% occlusion of the left anterior descending coronary artery proximal to the first septal perforating branch, and patients with triple-vessel or left main coronary artery obstruction, manifested significantly greater diminution in ejection fraction during exercise (average diminution −10%) than did patients with less severe disease (single- or double-vessel occlusions excluding the proximal left anterior descending, average diminution −3%, p <0.001). In contrast, the magnitude of ejection fraction changes during cold stimulation was indistinguishable among patients in the 2 angiographically defined subgroups (NS, Fig. 6, Table I). Moreover, the magnitude of ejection fraction diminution among patients with severe lesions (left main and proximal left anterior descending) was markedly and significantly (p <0.05) greater during exercise than during cold stress, whereas the magnitude of diminution was indistinguishable when the 2 stresses were applied to patients with angiographically less severe obstruction.

Nonetheless, 4 patients with fixed obstructive CAD manifested markedly greater diminution in ejection fraction (difference >5%, the error of the method,[3,20,21] between the 2 stresses) when cold was applied than when exercise was performed (exercise change in ejection fraction 4.3 ± 3.0, cold change in ejection fraction −5.8 ± 3.1, p <0.001). In 1 of these patients with right coronary obstruction alone, regional dysfunction and a 4% decrease in ejection fraction occurred during cold stimulation with no regional dysfunction and a normal increase (8%) in ejection fraction during exercise. These 4 patients could not be distinguished from other patients (in whom exercise caused the greater diminution in ejection fraction) on the basis of absolute or relative heart rate or arterial pressure responses to the 2 stresses.

Discussion

Our data indicate that although cutaneous cold stimulation can produce ischemic changes detectable by radionuclide cineangiography in a majority of patients with fixed obstructive CAD, this form of stress is less effective in producing such changes than is supine bicycle exercise. Thus, the production of regional dysfunction during stress, previously noted to be a highly specific indicator of CAD,[3–10,22] was present in 57% of our patients when cold stimulation was employed, but was present in 81% during bicycle exercise. Moreover, although evidence of global left ventricular dysfunction, indicated by the abnormality of stress-induced change in left ventricular ejection fraction, was present in most patients when either stress was applied, the magnitude of stress-induced changes in normal subjects and in patients with CAD was significantly more easily distinguished when exercise, rather than cold stimulation, was employed. As a result, when the presence of either regional dysfunction or specific changes in ejection fraction was employed as a diagnostic criterion, patients with fixed obstructive CAD were more accurately detected during exercise than during cold stress.

Our results are consistent with the preliminary findings of Wynne et al[23] who evaluated 15 patients with fixed obstructive coronary disease as well as 5 normal subjects. To define the expected response of left ventricular ejection fraction to cold stimulation in normal subjects, systolic blood pressure was increased with methoxamine to levels noted during cold stimulation, and ejection fraction was measured by echocardiography. Applying these methods, Wynne et al[23] determined that ejection fraction could be expected to decrease an average of 4% and a maximum of 10%, with 95% confidence limits. Using this criterion for normal response, Wynne et al[23] found that the sensitivity of radionuclide cineangiography was 33% and the specificity 80% when

cold stimulation was employed. No comparison with results obtained during exercise was performed.

Preliminary results of assessment of 24 patients and 18 normal subjects by Manyari et al[14] indicated sensitivity (38%) similar to those of Wynne et al[23] when cold stimulation was employed with ejection fraction criteria (ejection fraction decrease >6%) for diagnosis. In addition, Manyari et al[14] evaluated the relative response of their patients during exercise and reported results similar to those of the present study (exercise sensitivity 79%) although the specific diagnostic ejection fraction criteria employed were not reported. Neither our results nor those of Wynne or Manyari and their co-workers are quantitatively similar to those of Wainwright et al[13] who found a very pronounced separation of normal subjects and patients with fixed obstructive disease when ejection fraction criteria were applied to the results of radionuclide cineangiography during cold stimulation. Wainwright et al[13] also found radionuclide cineangiography during cold stimulation to be superior to single-lead exercise electrocardiography in detecting patients with fixed obstructive CAD, also inconsistent with our findings. However, Wainwright et al[13] assessed only 12 patients in their comparative study, and the quantitative differences between their results and those of other investigators may have resulted from variations in patient selection within the relatively small study groups in most reports.

Our findings are nonetheless consistent with those of Wainwright et al[13] in that, particularly when we employed regional function determination for purposes of diagnosis, cold stimulation was effective in identifying a significant number of patients with fixed obstructive CAD. These results suggest that cold stimulation may be a useful alternative to exercise testing for this purpose. The mechanisms by which cold stimulation produces myocardial ischemia are not completely understood. Previous investigations indicate that cutaneous application of cold acts through an alpha-adrenergic reflex arc to cause systemic vasoconstriction and thereby to increase total peripheral resistance.[11–13,24,25] The increase in vascular resistance, with the resulting increase in systemic arterial pressure, occurs without the development of reflex bradycardia in most patients and therefore almost invariably increases myocardial oxygen demand. Thus, cold stimulation potentially causes an imbalance between myocardial oxygen supply and demand in patients with fixed obstructive disease. Of note, however, in contrast to the response noted during bicycle exercise, very little increase in heart rate occurs during cold stimulation. Therefore, myocardial oxygen consumption, as indicated by the rate-pressure product, is significantly higher during bicycle exercise than during cold stimulation, perhaps accounting at least in part for the greater accuracy of radionuclide cineangiography in detecting patients with fixed obstructive CAD when exercise is employed.

However, although increases in myocardial oxygen demand may account for the ischemic changes seen during cold stress in patients with fixed obstructive disease, recent reports suggest that cold stimulation also may produce myocardial ischemia by restricting myocardial oxygen supply.[24,25] Thus, Neill et al[12] observed that cold exposure provoked angina and lactate production when the rate-pressure product was significantly lower than that associated with angina during atrial pacing. Consistent with these findings and using direct measurements of coronary vascular resistance, Mudge et al[11] documented an increase both in systemic and coronary resistance in patients with fixed obstructive CAD during cold stimulation, with a concomitant reduction in coronary flow in 3 patients and with the development of angina in 4 of 12 patients; conversely, during atrial pacing to ischemia and angina, coronary resistance decreased and coronary blood flow increased.[25] Normal subjects, despite systemic arterial vasopressor responses similar to those in patients, all had decreased coronary vascular resistance during cold stimulation.[11]

Although the site of cold-mediated vasoconstriction theoretically might be the arteriolar or large arterial level, or both, Raizner et al[15] recently demonstrated cold-induced focal coronary artery spasm during arteriography in 7 of 35 patients with fixed obstructive lesions. Two of the 7 patients with spasm had chronic typical angina pectoris, indicating that at least in some patients with fixed obstructive disease, cold-induced ischemia may result in part from dynamic obstruction at the level of the large coronary arteries. Although this phenomenon is rare, it also appears to occur occasionally during exercise.[26] These results also suggest that a spectrum of coronary vascular reactivity to cold stimulation exists, and that this form of stress may be of particular utility in efforts to detect patients with a dynamic component of coronary artery obstruction. Of note in this regard are the preliminary data of Perez-Balino et al[27] who found regional abnormalities in 7 of 10 patients with documented spasm during cold stimulation when radionuclide cineangiography was performed. These findings suggest that radionuclide cineangiography may be of particular value in the noninvasive detection of patients with dynamic coronary artery obstruction during cold stimulation. Such a possibility is of potential clinical importance, because the current availability of calcium slow channel blocking agents may provide a therapy particularly well suited to patients whose ischemic disease is mediated in part by dynamic obstruction.[28–33] Further studies will be necessary to determine the clinical importance of these speculations.

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Ischemia-Associated Intraventricular Conduction Disturbances During Exercise Testing as a Predictor of Proximal Left Anterior Descending Coronary Artery Disease

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To determine the incidence and significance of transient intraventricular conduction abnormalities occurring in association with myocardial ischemia during exercise testing, the recordings of 2,200 consecutive exercise tests were reviewed. Ten patients (0.45%) were identified as having both ischemia and intraventricular conduction abnormalities that developed transiently during the exercise test. In all 10 patients both typical angina and electrocardiographic evidence of ischemia developed during exercise. Among the 10 patients, left anterior hemiblock developed in 4, left posterior hemiblock in 2, right bundle branch block (RBBB) in 2, RBBB with left axis deviation in 1, and left anterior hemiblock progressing to complete left bundle branch block (LBBB) in 1. All 10 patients had cardiac catheterization showing significant obstruction of the left anterior descending (LAD) coronary artery at or before the origin of the first septal branch. Eight patients were treated surgically and 2 medically, all with relief of ischemic symptoms. Nine of the 10 had repeat exercise stress testing without angina or electrocardiographic evidence of ischemia and without recurrence of the transient intraventricular conduction disturbance.

It is concluded that the development of transient intraventricular conduction abnormalities associated with myocardial ischemia during exercise testing is an uncommon occurrence (0.45%). When such conduction disturbances do develop, the existence of significant disease in the proximal portion of the LAD coronary artery is strongly suggested. With control of myocardial ischemia, the transient conduction disturbances during exercise are ameliorated.

Exercise electrocardiography is widely used in evaluating patients with coronary artery disease. Although the significance of S-T segment changes is widely appreciated, less common abnormalities such as transient conduction defects may also occur. However, the incidence of transient intraventricular conduction abnormalities during exercise and their correlation with angiographic data have not been clarified.[1–5] We previously reported 2 cases of intermittent left anterior hemiblock during exercise-induced ischemia.[6] Both patients had significant obstruction of the proximal left anterior descending (LAD) coronary artery before or involving the origin of the first septal perforator branch. To put this observation in perspective, we reviewed a consecutive exercise test experience of 2,200 patients and analyzed the records of the 10 patients in the group, including the 2 previously reported on, in whom transient intraventricular conduction abnormalities developed in association with myocardial ischemia during exercise. The incidence and clinical significance of this finding are presented.

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Methods

Patient population: The electrocardiographic (ECG) records of the exercise stress tests that were performed on 2,200 consecutive patients over a 3-year period were reviewed. These represented all exercise tests performed at a large referral hospital and included tests performed to evaluate the presence and severity of coronary artery disease as well as the functional capacity of patients with cardiac disease. Ten patients (0.45%) had transient intraventricular conduction defects and evidence of myocardial ischemia. All 10 patients had both ECG evidence of myocardial ischemia and typical exertional angina. There were 8 male and 2 female patients aged 37 to 71 years (mean 51). Coronary artery bypass graft surgery was performed in 8, of whom 7 underwent repeat exercise testing within 1 to 3 months. Two patients were managed with medical therapy and both underwent repeat exercise testing within 3 months. There were 4 patients in the total group of

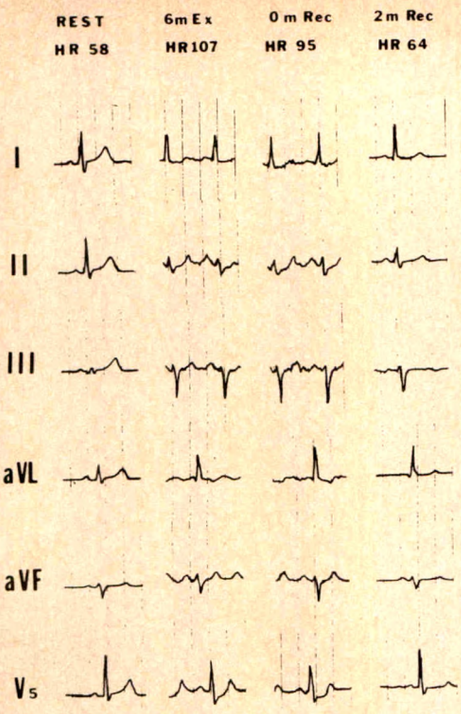

FIGURE 1. Twelve-lead electrocardiogram of a patient in whom left anterior fascicular block developed at the sixth minute of exercise. The conduction disturbance disappeared by the second minute of recovery. Ex = exercise; HR = heart rate; Rec = recovery.

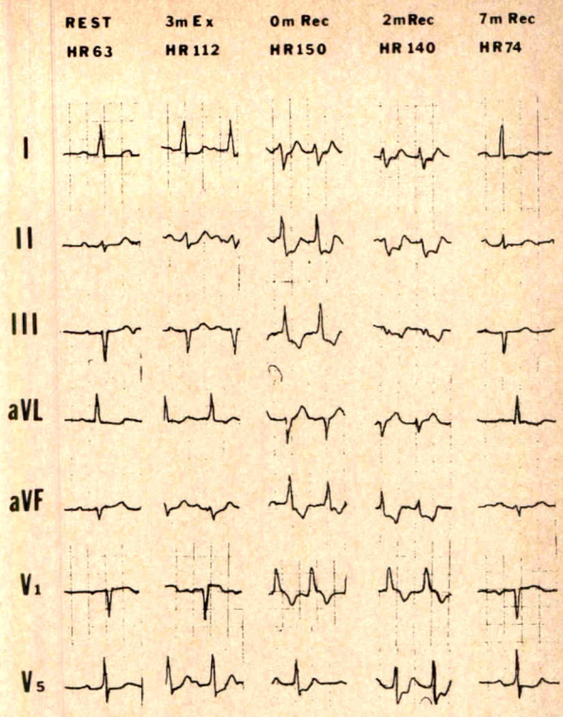

FIGURE 2. Twelve-lead electrocardiogram of patient 5 in whom left posterior fascicular block developed after 6 minutes of exercise. The electrocardiogram has returned to control after the seventh minute of recovery. Ex = exercise; HR = heart rate; Rec = recovery.

2,200 in whom rate-related conduction disturbances developed. In 3 of these patients left anterior hemiblock developed and in 1, left bundle branch block developed. None of the 4 had either angina or S-T changes suggesting myocardial ischemia. None was diagnosed as having coronary artery disease. These patients received no therapy and on repeat exercise testing they had reproducible rate-related intraventricular conduction disturbances. They were not included in the study population because of the intention of defining the significance of those transient intraventricular conduction disturbances that were associated with myocardial ischemia.

Exercise protocol: Nine patients had exercise testing using the Bruce multistage treadmill protocol,[7] and 1 patient was exercised using the United States Air Force School of Aviation Medicine protocol.[8] Before the test, blood pressure and heart rate were taken with the patient in the supine and upright position. During exercise, continuous ECG monitoring was performed using 3 leads. Blood pressure, heart rate, and 12-lead electrocardiogram were obtained at 1-minute intervals throughout exercise and for 5 minutes after exercise. The patients exercised to a symptom-limited endpoint such as severe angina pectoris, fatigue, shortness of breath, hypotension, or severe ventricular dysrhythmia.

An ischemic ECG response was defined as 1.0 mm of horizontal or downsloping S-T segment depression that persisted for at least 0.08 second.[9,10] The mean QRS axis in the frontal plane was determined using the method described by Laiken et al[11] in which the QRS axis is obtained from any 1 of 3 different lead combinations using a single, compact table. The time of occurrence and the duration of the conduction disturbances were noted as was the intraventricular conduction time.

The fascicular blocks were diagnosed using the criteria prepared by the Criteria Committee of the New York Heart Association.[12] Left anterior hemiblock is diagnosed in the presence of marked left axis deviation (−45° to −90°) and an increase of no more than 0.02 second over the original QRS duration. In addition, there must be a q in leads I and aVL and an rS in leads II, III, and aVF. Left posterior hemiblock is diagnosed in the presence of right axis deviation (+90° to 100°), minimal change in QRS duration which is 0.09 to 0.10 second, and a qR in leads II, III, and aVF. This diagnosis was made after exclusion of right ventricular enlargement, emphysema, and extensive lateral wall myocardial infarction by physical examination, 12-lead electrocardiogram, and chest X-ray.

Catheterization protocol: All patients underwent cardiac catheterization within 1 to 2 weeks after the initial treadmill test. Left heart catheterization was performed through the percutaneous femoral approach. Left ventricular cineangiograms and selective coronary arteriograms were recorded on 35 mm film at 60 frames/s using a cesium iodide image-intensifier system. Coronary arterial stenosis was estimated as a percentage decrease in luminal diameter. Stenosis >70% was considered hemodynamically significant. Left ventricular volumes and ejection fraction were calculated from the right anterior oblique ventriculogram using the area-length method.[13]

Statistical analysis: The results of the exercise test were expressed as the mean ± standard deviation. The results before and after exercise were compared using a paired t test.

Results

Ten of 2,200 patients (0.45%) undergoing an exercise tolerance test had intermittent intraventricular conduction disorders in association with myocardial ischemia. These included left anterior hemiblock in 4 patients (Fig. 1), left posterior hemiblock in 2 (Fig. 2),

TABLE I Clinical Data

Pt	IVCD	Age (yr) & Sex	Previous MI	Angina	Medication
1	LAH	59M	0	+	IDN, NTG, P
2	LAH	37M	0	+	0
3	LAH	51M	0	+	IDN, P
4	LAH	50M	0	+	0
5	LPH	71M	+	+	IDN, P
6	LPH	62M	0	+	IDN, P
7	RBBB	52M	0	+	0
8	RBBB	41F	0	+	0
9	RBBB/LAD	52M	0	+	0
10	LAH/LBBB	40M	0	+	IDN, NTG

IDN = isorbide dinitrate; IVCD = intraventricular conduction defects; LAD = left axis deviation; LAH = left anterior hemiblock; LPH = left posterior hemiblock; LBBB = left bundle branch block; MI = myocardial infarct; NTG = nitroglycerin; P = propranolol; Pt = patient; RBBB = right bundle branch block; 0 = no; + = yes.

right bundle branch block (RBBB) in 2, RBBB with left axis deviation in 1, and left anterior hemiblock progressing to complete left bundle branch block (LBBB) in 1. The clinical data in these patients are shown in Table I. As shown in this table, no patient was receiving any drug known to prolong the QRS duration. The individual and mean exercise test results are shown in Table II. The results shown in this table for the exercise electrocardiogram represent the heart rate, QRS axis, and QRS duration at the time of onset of the conduction disturbance. In Patients 1 through 9, these data represent the initial and sole conduction disturbance. In Patient 10 the values are those that existed at the time of development of complete LBBB. In all patients angina and ECG evidence of ischemia developed during exercise and in all 10 patients the chest pain and S-T changes occurred before the development of the intraventricular conduction disturbance. A hemiblock alone developed in 6 patients, and in 4 patients complete bundle branch block developed. The mean QRS was 0.085 at rest and increased during exercise to 0.110 second ($p < 0.01$). The onset of the intraventricular conduction defect occurred after an average of 5.6 minutes of exercise (range 3 to 12) and the conduction defect persisted an average of 3.1 minutes (range 1.5 to 9). In all 10 patients the conduction defect persisted for the remainder of exercise and disappeared only during the recovery period. Table II shows the exercise time at the onset of the conduction defect as well as the time of duration of the conduction defect in each patient.

Catheterization data: Left ventriculography and coronary arteriography data are shown in Table III. The left ventricular ejection fraction was reduced (<0.50) in 3 patients, but the mean value for the group was 0.56 ± 0.08 which is within the normal range of 0.64 ± 0.07 previously reported from our laboratory.[14] All 3 patients with a low ejection fraction and 4 of 7 patients with a normal ejection fraction had regional wall motion abnormalities, particularly in the anterior and apical segments. All 10 patients had significant obstruction of the LAD coronary artery before or at the origin of the first septal branch (Fig. 3). Three patients had single-vessel disease, 3 had double-vessel involvement, and 4 had triple-vessel disease. Two patients had stenosis of the left main coronary artery and these 2 patients had left posterior hemiblock during exercise. Three patients had collateral circulation whereas in the other 7, collateral circulation was absent.

Follow-up evaluation: Nine of the 10 patients were reevaluated by exercise testing within 3 months of coronary bypass surgery or the institution of medical therapy. All demonstrated improvement in terms of a longer duration of exercise and a higher attainable maximal heart rate. The resting mean heart rate was 75 ± 8 beats/min and increased to 142 ± 22 beats/min with exercise ($p < 0.001$). No patient developed a significant axis shift with exercise with the mean QRS axis at rest being +70° and during exercise +77° (p not significant [NS]). In no patient did intraventricular conduction abnormalities develop during exercise. All patients exercised without developing angina or S-T segment abnormalities.

Discussion

Exercise-induced intraventricular conduction defects in association with myocardial ischemia were an uncommon finding in our laboratory (0.45% of cases) and represented a spectrum of defects. The most common was left anterior hemiblock. Rosenbaum et al[15] reported the first 5 cases of intermittent left anterior hemiblock. In 2 of their cases the cause was coronary artery disease, particularly LAD disease, and this association has been confirmed by several investigators.[1–5,6,16] All 4 of our patients with left anterior hemiblock had significant

TABLE II Treadmill Data

	Resting ECG			Exercise ECG			Exercise Performance		
Pt	HR (beats/min)	QRS Axis (degrees)	QRS Duration	HR	QRS Axis	QRS Duration	Onset of IVCD (min)	Duration of IVCD (min)	Type of IVCD
1	58	+37	0.09	90	−50°	0.09	5	9	LAH
2	60	+53	0.08	166	−67°	0.08	6	2	LAH
3	55	+11	0.10	107	−46°	0.10	5	2	LAH
4	75	+78	0.08	125	−135°	0.09	4.5	3	LAH
5	68	+30	0.08	140	+110°	0.10	6	2	LPH
6	62	+23	0.08	94	+100°	0.12	6	3	LPH
7	83	+81	0.09	140	−150°	0.12	4	2.5	RBBB
8	75	+68	0.09	125	−111°	0.14	12	1.5	RBBB
9	72	+90	0.08	140	−40°	0.12	3	3	RBBB/LAD
10	71	+113	0.08	107	−77°	0.14	5	3	LAH/LBBB

ECG = electrocardiogram; HR = heart rate. Other abbreviations as in Table I.

obstruction of the LAD artery proximal to or at the origin of the first septal branch. In all 4 patients the conduction defect was accompanied by ECG manifestations of myocardial ischemia, and the conduction disturbance resolved when the ischemia subsided.

Left posterior hemiblock was a less common transient abnormality in our study. Hegge et al[1] reported right axis deviation during exercise in 9 patients, but only 3 of them fulfilled the ECG criteria for left posterior hemiblock. One of their patients had significant disease of the left main coronary artery and 2 had significant obstruction of the LAD and right coronary arteries. Bobba et al[5] reported on 4 patients with transient left posterior hemiblock during exercise. All of them had significant disease of the proximal right coronary artery and 2 had significant disease of the left coronary artery.

Exercise-induced complete bundle branch block occurred in 4 of our patients during exercise. All of them had significant proximal obstruction in the LAD coronary artery. We had 2 patients with transient RBBB. Whinnery et al[17] reported on a patient who had intermittent RBBB during exercise. However, that patient had no history of angina pectoris. The conduction abnormality was not associated with S-T abnormalities and persisted throughout the recovery period. At cardiac catheterization he had a normal LAD artery but 60% obstruction of the left circumflex coronary artery. Also, this patient was found to have persistent RBBB on subsequent Holter monitoring. The 2 patients with RBBB in the present study did have both angina and ECG evidence of ischemia during the exercise test and both had only transient occurrence of the conduction abnormality that resolved when the other signs of myocardial ischemia resolved. In 1 patient in the present study, transient left anterior hemiblock developed followed by complete LBBB during exercise. This association occurring in an acute setting has not previously been reported.

Transient bundle branch block during exercise is strongly related to reversible ischemia. This finding is in contrast to chronic RBBB[17,18] or LBBB[19] which may be an isolated conduction system abnormality. The response to bypass surgery with relief of ischemia and subsequent disappearance of the conduction abnormality confirms this observation. Very significantly, all 10 patients in this study in whom transient intraventricular conduction disturbances developed proved to have significant narrowing of the proximal portion of the LAD coronary artery. In 3 patients this was the only coronary lesion, whereas in 7 other patients coexistent lesions of other coronary arteries were present. Many clinicians attach a high degree of importance to lesions of the LAD artery proximal to the first septal perforator. In many centers such lesions are bypassed even if they are the sole lesion or the patient has only 2-vessel coronary artery disease. The justification given for this surgical approach is based on the large amount of myocardium, including the conduction system, that is placed at jeopardy by such lesions. The results of the present study indicate that the occurrence of intra-

FIGURE 3. Coronary arteriogram in the right anterior oblique position showing 95% coronary artery involving the origin of the first septal branch.

TABLE III Cardiac Catheterization Data

	Left Ventriculography		Coronary Angiography (% Diameter Reduction)				
Pt	EF	Regional Wall Motion	LM	LAD (Proximal)	LC	Right	Collateral Vessels
1	0.60	Ant hypokinesia	Normal	99	Normal	Normal	0
2	0.51	Apical hypokinesia after akinesia	Normal	95	95 1st OM	100	0
3	0.59	Normal	Normal	65	Normal	50% PD	0
4	0.46	Ant hypokinesia	Normal	100	75 1st OM	Normal	LAD fills from right
5	0.59	Ant hypokinesia and apical dyskinesia	95	95	75 1st and 2nd OM	Diffuse	0
6	0.42	Ant apical akinesia, inf hypokinesia	50	95	75 1st OM	100	PD fills from LAD
7	0.62	Ant and post hypokinesia	Normal	100	50 2nd OM	100	LAD fills from LC
8	0.60	Ant hypokinesia	Normal	95	Normal	Normal	0
9	0.68	Normal	Normal	95	Normal	80	0
10	0.60	Normal	Normal	90	Normal	Normal	0

Ant = anterior; EF = ejection fraction; LAD = left anterior descending; LC = left circumflex; LM = left main; OM = obtuse marginal; PD = posterior descending; post = posterior; Pt = patient.

ventricular conduction disturbances associated with myocardial ischemia during exercise testing is strongly suggestive of the presence of significant disease in the proximal portion of the LAD coronary artery.

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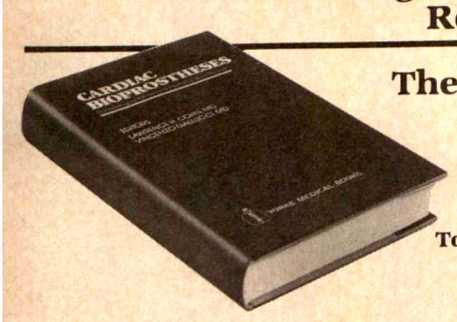
Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982



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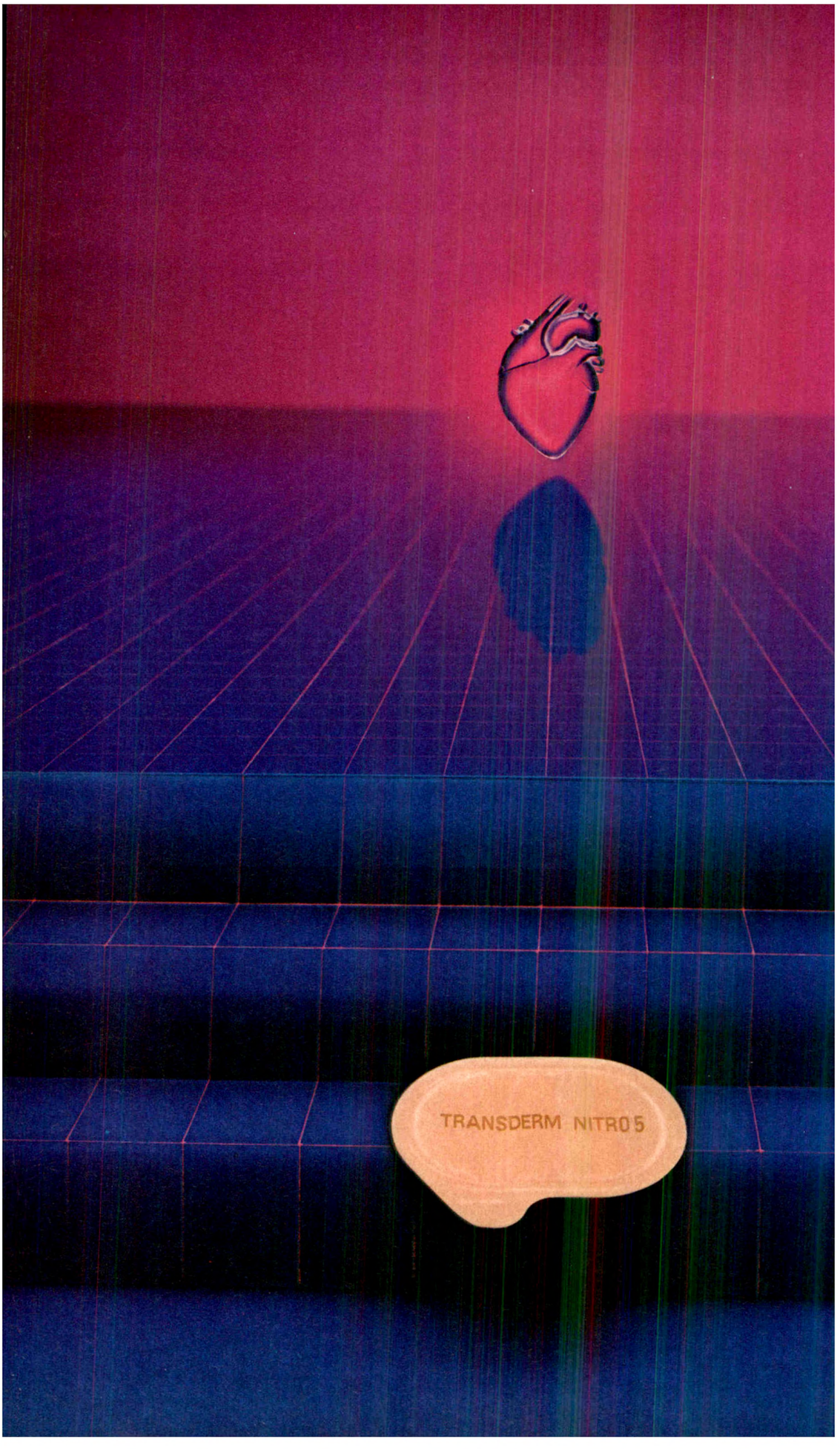
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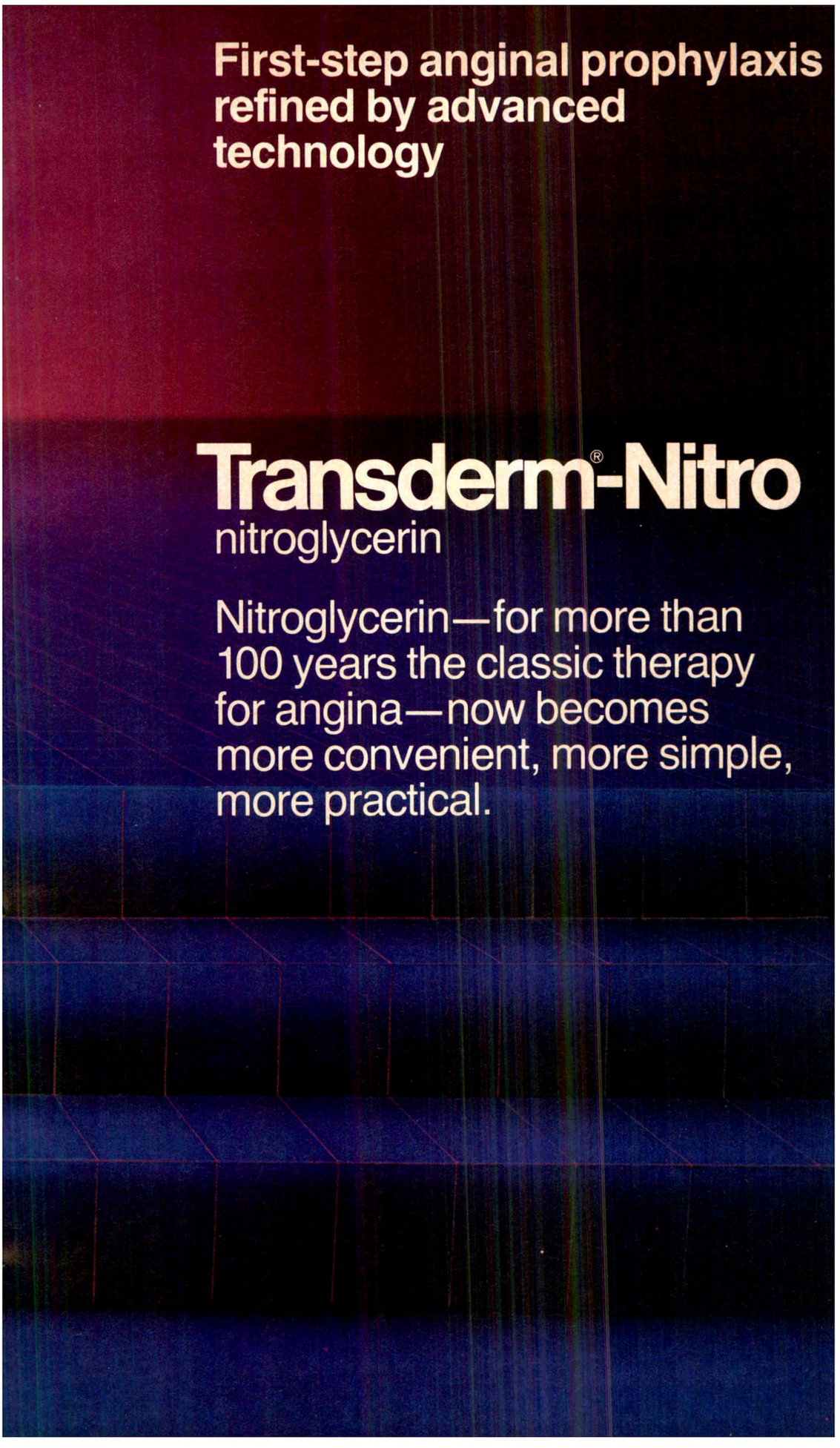
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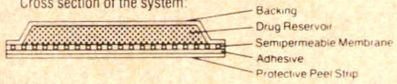
The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS

When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE

Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS

Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS

In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS

Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS

Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION

Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS

A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

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LOPID®
(gemfibrozil)

MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

Favorably regulates the balance of lipid fractions in certain dyslipidemias:

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transport cholesterol to the liver for catabolism and excretion)

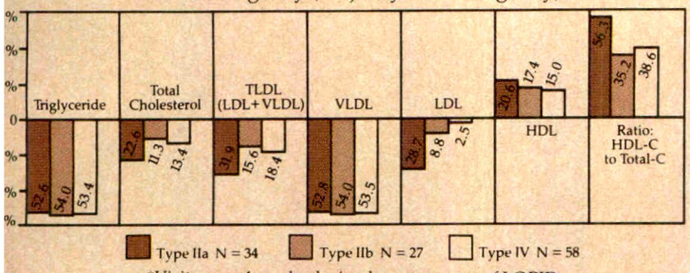
LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

Artist's interpretation of VLDL in bloodstream

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.
†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:
1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

LOPID®

300-mg capsules

(gemfibrozil)

PARKE-DAVIS

Please see following pages for brief summary of prescribing information.

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LOPID®
(gemfibrozil)
A LIPID REGULATOR

LOPID® (gemfibrozil) Capsules

Before prescribing, please see full prescribing information.
A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

0669G011

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Morris Plains, New Jersey 07950

PD-56-JA-1333-P-1 (11-82)

Determinants of the Incidence and Severity of Ventricular Arrhythmias in Aortic Valve Disease

KLAUS v. OLSHAUSEN, MD, FRANZ SCHWARZ, MD, JÖRG APFELBACH, NORBERT RÖHRIG, MD, BURKHARDT KRÄMER, MD, and WOLFGANG KÜBLER, MD,
With the technical assistance of SONJA GUND

The incidence of ventricular arrhythmias in patients with aortic valve disease was investigated. Twenty-four-hour ambulatory electrocardiographic recordings were obtained in 93 patients without coronary artery disease (aortic stenosis [AS], n = 38; combined AS and aortic regurgitation [AR], n = 27; and AR only, n = 28). The arrhythmias were compared with the hemodynamic findings of cardiac catheterization. Ventricular premature beats (VPB) were noted in 78 patients (84%). They were rare (<100 VPB/22 hours) in 40 patients (43%), moderately frequent (101 to 1,000 VPB/22 hours) in 23 patients (25%), and frequent (>1,000 VPB/22 hours) in 15 patients (16%). Multiformity was found in 47 (51%), paired VPB in 32 (34%), and ventricular tachycardia in 17 (18%) of the 93 patients studied. The occurrence of ventricular arrhythmia was not related to the type of valve lesion, to the transvalvular gradient in patients with AS, or to the degree of regurgitation in patients with AR. In contrast, the grade of arrhythmia showed a negative correlation with left ventricular ejection fraction (AS, $r_s = -0.58$; AS and AR, $r_s = -0.67$; AR, $r_s = -0.78$; all $p < 0.001$) and a positive correlation with peak systolic left ventricular wall stress (AS, $r_s = 0.56$; AS and AR, $r_s = 0.56$; AR, $r_s = 0.57$; all $p < 0.001$). The frequency of VPB also showed a negative correlation with left ventricular ejection fraction (AS, $r_s = -0.63$; AS and AR, $r_s = -0.65$; AR, $r_s = -0.71$; all $p < 0.001$).

This study indicates that ventricular arrhythmias are present in a large number of patients with aortic valve disease. The severity of arrhythmias is strongly influenced by myocardial performance. Thus, severe arrhythmias are frequently a sign of impaired left ventricular function.

Sudden cardiac death is a well-known complication in patients with aortic stenosis (AS).[1] Although malignant ventricular tachyarrhythmias are proposed as a cause of these lethal outcomes,[2] there is little detailed information about the incidence and severity of ventricular arrhythmias in patients with AS or aortic regurgitation (AR). This study investigates the incidence and severity of ventricular arrhythmias in 93 patients with isolated aortic valve disease (without coronary artery disease) by 24-hour ambulatory electrocardiographic monitoring. These findings were related to hemodynamic data as assessed by cardiac catheterization to analyze the factors influencing the occurrence of ventricular arrhythmias in aortic valve disease.

From the Medizinische Universitätsklinik, Abteilung Innere Medizin III (Kardiologie), Heidelberg, West Germany. This study was supported in part by the Deutsche Forschungsgemeinschaft (Bad Godesberg) within the SFB 90- Kardiovaskuläres System, University of Heidelberg. Manuscript received August 31, 1982; revised manuscript received December 21, 1982, accepted December 22, 1982.

Address for reprints: Klaus v. Olshausen, MD, Innere Medizin III, Bergheimer Strasse 58, D-6900 Heidelberg, West Germany.

Methods

Patients: All 93 patients with aortic valve disease were studied between July 1980 and July 1982. Seventy-six were men and 17 were women; their ages ranged from 18 to 70 years (mean 50 ± 13). A patient was included in the study if the following criteria were fulfilled: (1) presence of isolated aortic valve disease, without previous surgical treatment; (2) absence of coronary heart disease (proven by selective coronary angiography); that is, patients with ≥25% luminal narrowing of a major coronary vessel were excluded; (3) normal serum potassium level (3.5 to 5.0 mEq/liter) on the day of ambulatory monitoring (±24 hours); and (4) absence of specific antiarrhythmic therapy.

Cardiac catheterization: All 93 patients were studied by right- and left-sided cardiac catheterization including coro-

TABLE I Reproducibility of Ambulatory Electrocardiographic Recordings

Patient	First Recording				Second Recording			
	VPB/22 h	Couplets	VT	Grade	VPB/22 h	Couplets	VT	Grade
1	1	0	0	1	0	0	0	0
2	4	0	0	1	0	0	0	0
3	13	0	0	1	8	0	0	1
4	1	1	0	4A	4	0	0	1
5	38	1	0	4A	30	0	0	3
6	178	0	0	3	238	1	1	4B
7	1,362	0	0	3	1,482	1	1	4B
8	275	0	0	3	1,323	1	0	4A
9	3,567	16	0	4A	465	1	0	4A
10	1,194	60	1	4B	523	25	0	4A
11	1,069	2	1	4B	722	0	0	3
12	6,608	338	3	4B	5,118	198	3	4B
Mean	1,192 ± 1,996	...	...	3.1 ± 1.4	826 ± 1,446	...	...	2.8 ± 1.8

Grade = highest grade of ventricular arrhythmia; VPB = ventricular premature beat; VT = ventricular tachycardia.

nary angiography. An 8.5F Brockenbrough catheter was positioned by transseptal puncture into the left ventricle and a pigtail catheter (7F) was positioned retrogradely into the aortic root. Pressures were recorded before injection of contrast medium. Single-plane 35 mm cineangiograms of the left ventricle were filmed (50 ml Urografin® 76, 50 frames/s, 30° right anterior oblique projection, Philips image intensifier system). Left ventricular volumes and left ventricular ejection fraction were calculated using the computer-aided area-length method (system Mennen-Greatbatch).

The orifice area of the aortic valve in patients with pure AS was calculated using the formula of Gorlin et al.[3] It was normalized to body surface area. The severity of AR was assessed by aortic root angiography.[4] The cardiac index was determined by the Fick principle. Peak systolic left ventricular wall stress was calculated according to the method of Gaasch et al.[5]

Patients with a calculated valve area ≤ 0.6 cm^2/m^2 and AR of less than grade 2+ of 4+ grades were classified as having AS. Patients with a regurgitation of grade $\geq 2+$ and a transvalvular gradient <25 mm Hg were classified as having predominant AR. Patients who did not meet these criteria were classified as having combined AS and AR.

Ambulatory electrocardiographic monitoring: Within 48 hours before or after cardiac catheterization, an ambulatory electrocardiographic monitoring with a mean duration of 22 hours (range 18 to 25) was performed. The ambulatory electrocardiogram was recorded on a 1-channel Oxford Medilog Mark I recorder using a bipolar V_1 to V_5 lead system. The recordings were analyzed semiautomatically using the Reynolds Pathfinder system and a Digital PDP 11/03 computer with 2 floppy discs. During automatic analysis all tapes were simultaneously scanned visually on the oscilloscope by an experienced technician. When arrhythmia was suspected, that portion of the tape was printed out. Examples of all types of ventricular premature beats (VPB), couplets, and ventricular tachycardia were printed on paper and interpreted by a cardiologist.

The accuracy of the Medilog-Pathfinder system in detecting VPB and repetitive arrhythmias was validated recently.[6–8] In a study of 31 1-hour electrocardiographic recording segments, system output was compared with a beat-by-beat hand count of the electrocardiogram. These segments contained 139,583 normal beats and 9,146 VPB. The predictive value was 97% for VPB and 92% for paired VPB and ventricular tachycardia. The sensitivity was 95% and 92%, respectively. The false-positive rate was 2.7% for VPB.[6]

A modified Lown grading system as described by Ryan et al[9] for ventricular arrhythmias was used: grade 0, no VPB in 22 hours; grade 1, occasional VPB but ≤30 in any hour of monitoring; grade 2, >30 VPB in any hour of monitoring; grade 3, multiform VPB; grade 4A, couplets (2 consecutive VPB); grade 4B, ventricular tachycardia (≥3 VPB in succession with a frequency >100/min).

Statistical analysis: Data are expressed as mean values ± standard deviation. The correlations between ventricular arrhythmias (incidence of VPB, grade of ventricular arrhythmia) and clinical and hemodynamic data were performed by calculating the rank correlation coefficient r_s of Spearman.[10] If more than 20% ties occurred, the modification of Kendall was applied.[10] With 2-tailed testing, a probability value <0.05 was considered significant.

For calculation purposes, the grade 4A of ventricular arrhythmia was assigned the value 4.0 and the grade 4B the value 4.5. All other grades were assigned their related numbers. Three or more mean values of ranks were compared by means of the H-test by Kruskal and Wallis.[10] Mean values of hemodynamic variables were compared by means of the t test for unpaired data.[10]

Results

Clinical and hemodynamic data: The functional class of the patient was determined according to the New York Heart Association classification.[11] Thus, 2 patients were determined to be in class I, 14 in class II, 62 in a class III, and 15 in class IV. Thirty-eight patients had AS, 27 patients had AS and AR, and 28 patients had AR. The mean functional class yielded no significant difference between the 3 groups (AS, 2.9 ± 0.7; AS and AR, 3.1 ± 0.6; and AR, 3.0 ± 0.6). The mean age of the patients with AS was 53 ± 14 years, of the patients with AS and AR, 49 ± 11 years, and of the patients with AR, 47 ± 11 years. These differences in age were insignificant.

The mean transvalvular aortic gradient was 94 ± 37 mm Hg in patients with AS, and 85 ± 33 mm Hg in patients with AS and AR. The mean aortic valve area normalized to body surface area was 0.28 ± 17 cm^2/m^2 in patients with AS. The mean degree of regurgitation was 2.9 ± 0.8 in patients with AS and AR and 3.4 ± 0.6 in patients with AR. The mean left ventricular ejection fraction was 66 ± 16% in patients with AS, 54 ± 18% in

TABLE II Distribution of Ventricular Premature Beat (VPB) Frequency

	All (n = 93)		AS (n = 38)		AS + AR (n = 27)		AR (n = 28)	
VPB/22 hours	n	%	n	%	n	%	n	%
0	15	16	6	16	2	7	7	25
1–100	40	43	21	55	11	41	8	29
101–1,000	23	25	4	11	10	37	9	32
>1,000	15	16	7	18	4	15	4	14

AR = aortic regurgitation; AS = aortic stenosis.

patients with AS and AR, and 60 ± 13% in patients with AR.

The electrocardiogram at rest revealed sinus rhythm in all patients except 2 with AS who had atrial fibrillation. Five patients had left bundle branch block (3 with AS, 2 with AS and AR). Two patients had right bundle branch block (1 with AS and AR, 1 with AR).

Reproducibility of ambulatory electrocardiographic monitoring (Table I): To assess spontaneous variability in arrhythmia frequency in patients with aortic valve disease, we evaluated two 24-hour ambulatory electrocardiographic recordings registered within 1 week in 12 patients. For the study, the results of the first recording were taken. Comparison of the 2 recordings revealed that the mean VPB frequency/22 hours decreased from 1,192 to 825, due mainly to a marked reduction in VPB in Patient 9, who had ventricular bigeminy in the first recording. The mean value of the highest grade of arrhythmia decreased from 3.1 to 2.8 (difference not significant [NS]); only 3 patients remained in the same grade (Patients 3, 9, and 12). It is noteworthy that only 1 patient (Patient 4) had a change in grade from no or unifocal VPB (grades 0 to 2) to complex VPB (grades 3 to 4B), or vice versa. Thus, although 75% of these 12 patients had a change in their highest grade of arrhythmia, 92% remained in their group of no or unifocal (grades 0 to 2) or complex VPB (grades 3 to 4B).

Incidence of VPB (Table II): Fifteen patients (16%) had no ventricular arrhythmia noted during the recording period. In the remaining 78 patients (84%), VPB frequency ranged from 1 to 7,510 VPB/22 hours, with a mean value of 790 ± 1,588. Ventricular premature beats were rare (<100 VPB/22 hours) in 40 patients (43%), moderately frequent (101 to 1,000 VPB/22 hours) in 23 patients (25%), and frequent (>1,000 VPB/22 hours) in 15 patients (16%).

Incidence of VPB and left ventricular performance (Fig. 1): A highly significant inverse correlation was found between the left ventricular ejection fraction and the VPB frequency in all 3 study groups (AS, $r_s = -0.63$; AS and AR, $r_s = -0.65$; AR, $r_s = -0.71$; all $p < 0.001$) (Fig. 1). Other clinical and hemodynamic variables such as New York Heart Association func-

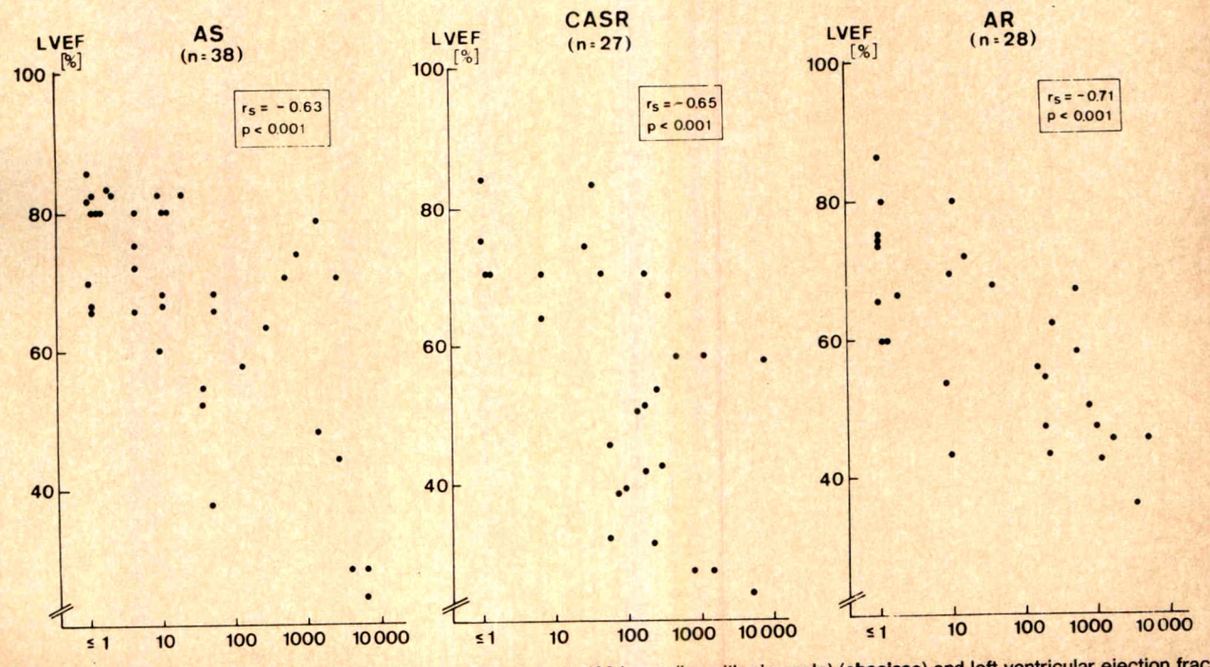

FIGURE 1. Relation between incidence of ventricular premature beats/22 hours (logarithmic scale) (**abscissa**) and left ventricular ejection fraction (LVEF) (**ordinate**). **Left panel,** 38 patients with aortic stenosis (AS). **Center panel,** 27 patients with combined aortic stenosis and regurgitation (CASR). **Right panel,** 28 patients with aortic regurgitation (AR).

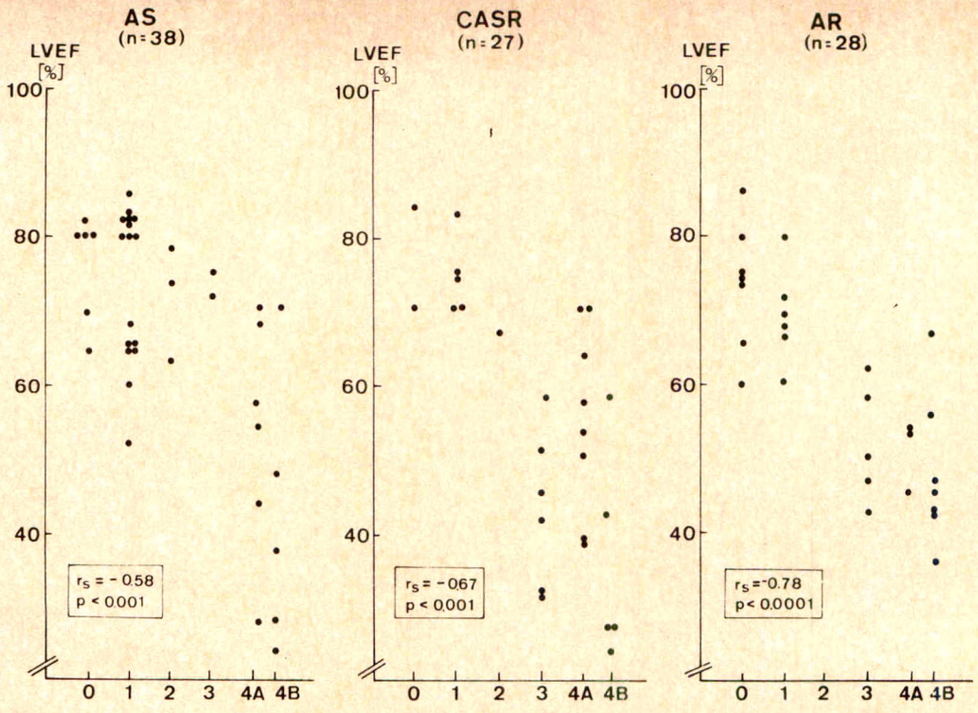

FIGURE 2. Relation between grade of arrhythmia (**abscissa**) and left ventricular ejection fraction (LVEF) (**ordinate**) in 38 patients with aortic stenosis (AS) (**left panel**), 27 patients with combined aortic stenosis and regurgitation (CASR) (**center panel**) and 28 patients with aortic regurgitation (AR) (**right panel**).

tional class, left ventricular end-diastolic pressure, cardiac index, and peak systolic left ventricular wall stress showed no or a weak (r_s <0.50) relation to VPB frequency. In particular, aortic gradient and aortic valve area in patients with AS and the degree of AR in patients with AR showed no correlation with VPB frequency.

Grade of ventricular arrhythmia (Table III): Seventy-eight patients (84%) had ventricular arrhythmias. Forty-four patients had ≤30 VPB in any 1 hour, and 34 patients had >30 VPB in at least 1 hour. Forty-seven (51%) patients had multiform and 32 (34%) had paired VPB. Seventeen (18%) patients had ventricular tachycardia. These differences were insignificant.

Grade of ventricular arrhythmia and left ventricular performance (Fig. 2 and 3): After selecting the highest grade of ventricular arrhythmia for each patient, we found a highly significant inverse correlation between the left ventricular ejection fraction and the grade of arrhythmia in all 3 groups (AS, $r_s = -0.58$; AS and AR, $r_s = -0.67$; AR, $r_s = -0.78$; all $p < 0.001$) (Fig. 2). All 24 patients with an ejection fraction <50% had complex VPB (grades 3 to 4B). A significant relation also was observed between peak systolic left ventricular wall stress and grade of arrhythmia in all 3 groups (AS, $r_s = 0.56$; AS and AR, $r_s = 0.58$; AR, $r_s = 0.57$; all $p < 0.005$) (Fig. 3).

Only weak correlations (r_s <0.50) were found between the highest grade of arrhythmia and the New York Heart Association functional class, left ventricular end-diastolic pressure, and cardiac index in all 3 groups. Particularly, there was no relation between the aortic gradient or aortic valve area and the highest grade of ventricular arrhythmia in patients with AS. The degree

TABLE III Distribution of the Grade of Ventricular Arrhythmia

	All (n = 93)		AS (n = 38)		AS and AR (n = 27)		AR (n = 28)	
Arrhythmia Grade*	n	%	n	%	n	%	n	%
0 (no VPB)	15	16	6	16	2	7	7	25
1 (≤30 VPB/hour)	44	47	22	58	14	52	8	29
2 (>30 VPB/hour)	34	37	10	26	11	41	13	46
3 (multiform VPB)	47	51	13	34	19	70	15	54
4A (couplets)	32	34	10	26	13	48	9	32
4B (VT)	17	18	5	13	5	19	7	25

* Classification of Ryan et al.[9]
AS = aortic stenosis; AR = aortic regurgitation; VPB = ventricular premature beats; VT = ventricular tachycardia.

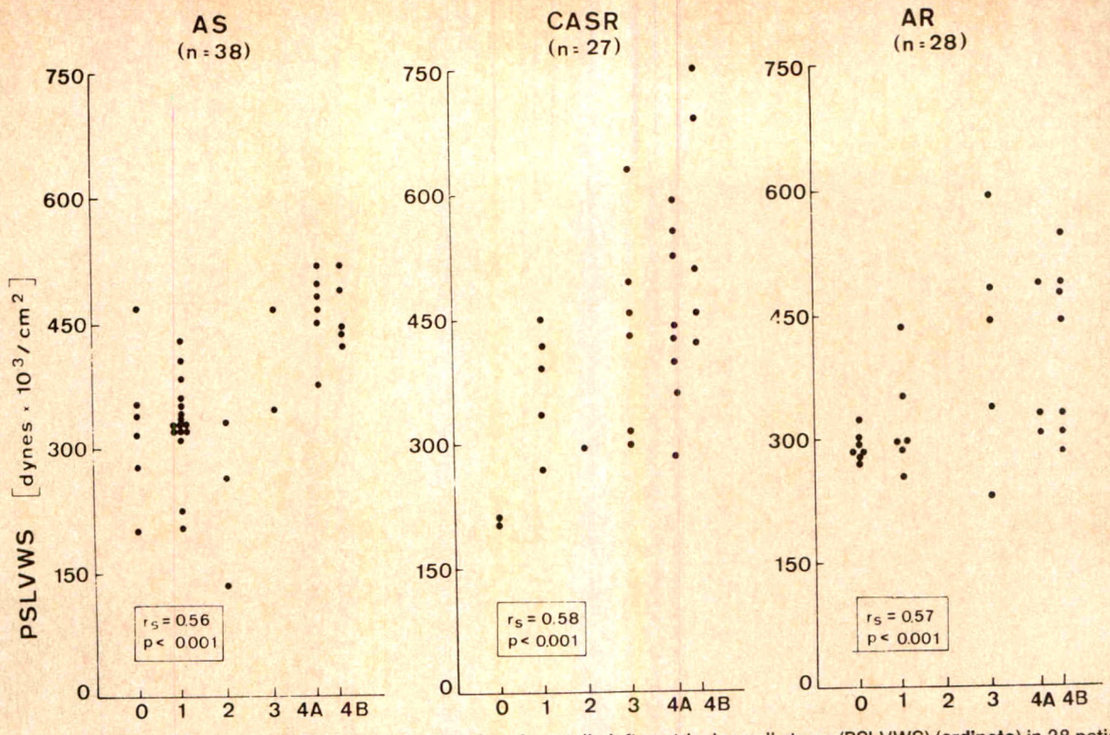

FIGURE 3. Relation between grade of arrhythmia (**abscissa**) and peak systolic left ventricular wall stress (PSLVWS) (**ordinate**) in 38 patients with aortic stenosis (AS) (**left panel**), 27 patients with combined aortic stenosis and regurgitation (CASR) (**center panel**) and 28 patients with aortic regurgitation (AR) (**right panel**).

of regurgitation in patients with AR also showed no relation to the highest grade of arrhythmia.

Ventricular tachycardia (Table IV): Table IV summarizes the clinical and ambulatory electrocardiographic findings in the 17 patients with ventricular tachycardia. Five patients had AS, 5 had AS and AR, and 7 had AR. Only 4 had syncope, but only Patient 61 had a syncopal episode during ambulatory monitoring. The 17 patients with ventricular tachycardia had a significantly lower left ventricular ejection fraction (42 versus 65%, $p < 0.01$), higher peak systolic left ventricular wall stress (468 versus 362 dynes $\times 10^3/cm^2$, $p < 0.001$), and a higher incidence of VPB (1,825 versus 390 VPB/22 hours, $p < 0.01$) than the 76 patients without ventricular tachycardia. All patients except 2 (Patients 16 and 89) also had paired VPB. Ventricular tachycardia in all except Patient 61 was nonsustained. Four patients had a single episode of ventricular tachycardia only, with a maximum of 5 beats; the longest nonsustained episode of ventricular tachycardia consisted of 12 beats. Long-term follow-up of the surviving 15 patients was not feasible since all underwent operation within 4 weeks.

None of the 93 patients died from heart failure, but 2 patients with ventricular tachycardia died suddenly. Patient 12 had sudden death within minutes at home (witnessed by his wife) while scheduled for operation the following week. The final arrhythmia could not be documented, but sudden death strongly suggests that a ventricular tachyarrhythmia was the reason for this lethal outcome. Patient 61, with severe AS and AR and a left ventricular ejection fraction of 24%, died suddenly in the hospital while awaiting operation. He was sitting and talking to his wife with no apparent anxiety or physical exertion when ventricular tachycardia with a frequency of 180 beats/min resulted in sudden death (Fig. 4).

Discussion

This study indicates that significant ventricular arrhythmias are common in patients with severe aortic valve disease. Left ventricular performance, as assessed by ejection fraction and peak systolic left ventricular

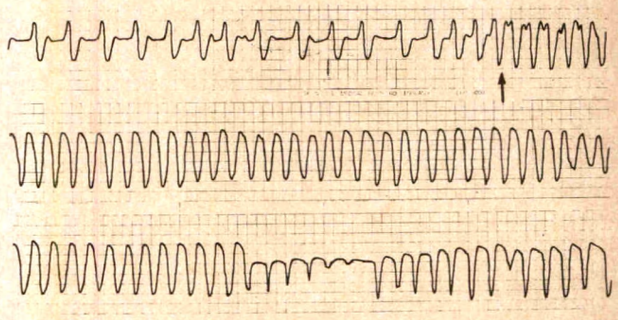

FIGURE 4. Ambulatory electrocardiographic recording at the time of the sudden cardiac death of Patient 61, who had severe combined aortic stenosis and regurgitation and reduced left ventricular function. Ventricular tachycardia developed suddenly (**arrow**), with a rate of 180 beats/min.

TABLE IV Summary of the Clinical, Hemodynamic and 24-Hour Ambulatory Electrocardiographic Findings in 17 Patients With Ventricular Tachycardia

Case	Lesion	NYHA	Syncope	LVEF	PSLVWS	Maximal VPB/hour	Total VPB/ 22 hours	Highest Grade of Ventricular Ectopic Activity*	Beats (n) in Longest Episode of VT (Episodes [n] of VT)
5	AS	3	−	28	432	625	5,727	4A	5 (3)
12†	AS	3	−	70	485	108	1,069	4A	3 (1)
16	AS	3	−	37	442	12	50	3	6 (2)
35	AS	4	−	24	420	521	6,608	4A	4 (3)
38	AS	4	+	48	515	253	1,588	4A	3 (5)
45	AS + AR	3	−	42	690	47	302	4A	5 (2)
50	AS + AR	4	−	27	453	106	1,380	4A	5 (4)
53	AS + AR	3	−	58	417	428	1,073	4A	5 (3)
61‡	AS + AR	3	+	24	506	827	5,220	4A	999 (2)
65	AS + AR	3	−	27	749	149	751	4A	5 (5)
70	AR	3	−	36	272	547	3,646	4A	5 (2)
74	AR	3	+	47	326	48	178	4A	3 (1)
76	AR	4	−	42	541	207	1,210	4A	3 (3)
85	AR	3	−	56	487	35	152	4A	12 (2)
87	AR	2	−	67	306	47	570	4A	4 (2)
89	AR	4	+	43	468	1	9	3	3 (1)
90	AR	4	−	45	442	150	1,194	4A	5 (1)
17 Patients with VT				42 ± 14§	468 ± 120‖		1,825 ± 2,154§		
76 Patients without VT				65 ± 17§	362 ± 95‖		390 ± 1,142§		

* Excluding grade 4B.
† Sudden cardiac death before operation.
‡ Died because of VT.
§ $p < 0.01$.
‖ $p < 0.001$.
AR = aortic regurgitation; AS = aortic stenosis; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PSLVWS = peak systolic left ventricular wall stress (dynes $\times 10^3/cm^2$); VPB = ventricular premature beat; VT = ventricular tachycardia.

wall stress, is the major determinant of the occurrence of complex ventricular arrhythmias.

Incidence and severity of ventricular arrhythmias: Frequent and complex ventricular ectopic activity was noted in 55% of the patients evaluated. Furthermore, 18% of the patients had ventricular tachycardia. Two of 17 patients with ventricular tachycardia died suddenly in the time between heart catheterization and their scheduled operations.

There are only a few preliminary studies on preoperative ventricular arrhythmias in patients with aortic valve disease. Kennedy et al[12] studied a small sample of 8 patients with AS and 7 patients with AR and found multiform VPB in 93% and ventricular tachycardia in 47%. They noted that the VPB frequency is rather low in patients with AS.

In another preliminary study, Schilling et al[13] described a marked prevalence of complex VPB in patients with aortic valve disease. In their study of 38 patients with AR, the grade of ventricular arrhythmia correlated with cardiac index, left ventricular end-diastolic pressure, and end-diastolic diameter.

Hochreiter et al[14] studied 28 patients with severe AR and could not detect a significant relation between the occurrence of complex VPB and left ventricular ejection fraction, although 10 of their 28 patients had multiform or repetitive ventricular arrhythmias. That only 38% of the patients exhibited complex VPB may be a hint that the patient group of this study is not comparable to our sample, in which 55% of patients with AR had complex VPB.

Klein et al[15] postulated that complex VPB in patients with AS may be associated with increased left ventricular wall stress. In 10 of their 26 patients with critical AS and complex VPB, they found increased left ventricular wall stress, whereas the mean ejection fraction did not differ in patients with grades 0 to 2 and grades 3 to 4B arrhythmias.

Role of left ventricular performance: In patients who survived myocardial infarction, a relation between left ventricular ejection fraction and the occurrence of complex ventricular arrhythmias has been demonstrated. Several investigators[16–18] have observed that the severity of ventricular arrhythmias may be related to both the number of stenotic coronary vessels and the extent of left ventricular dysfunction. The extent of fibrotic replacement of myocardium seems to be a major determinant of ventricular arrhythmias in patients who have had a myocardial infarction.

Our data indicate that in patients with AS, a high transvalvular gradient may not lead to complex ventricular arrhythmias as long as left ventricular performance is normal. The same applies to patients with AR: a high regurgitation volume may be tolerated by a normal left ventricle without the developmment of complex arrhythmias. However, there is considerable overlap: 23 (33%) of 69 patients with an ejection fraction >50% had complex VPB. This overlap was smaller in patients with AS than in patients with significant AR, indicating that an ejection fraction of 50% may already be a sign of impaired left ventricular function in patients with severe AR.[19]

In contrast, only 6 (25%) of 24 patients with an ejection fraction <50% had <100 VPB/22 hours, and all had complex VPB (grades 3 to 4B). Only 4 (9%) of all 47 patients with complex VPB had a peak systolic left ventricular wall stress <300 dynes $\times 10^3/cm^2$. Thus, reduced ejection fraction and high left ventricular wall

stess appear to be the major determinants of severe ventricular arrhythmia in aortic valve disease. In our study, these relations were demonstrated by highly significant correlation coefficients.

It has been shown that considerable changes in ultrastructure and augmentation of subendocardial fibrosis occur in patients with aortic valve disease with severe impairment of left ventricular performance.[20,21] These changes have been interpreted as morphologic correlates of myocardial ischemia and may be related to the occurrence of ventricular arrhythmias in these patients.

Significance of ventricular arrhythmias: Frequent and repetitive ventricular arrhythmias are associated with an increased risk of sudden cardiac death in patients who survived myocardial infarction.[22–25] In patients with aortic valve disease, it is unknown whether the occurrence of complex ventricular arrhythmias carries the same adverse implications. In patients with unoperated AS, the mortality rate due to sudden death has been found to be 15 to 20%, and of these patients only 3 to 5% were asymptomatic.[1] Sudden cardiac death also may occur in patients with significant AR (Patient 61). Schwartz et al[2] suggested a large left ventricle, a significant transvalvular gradient, and fibrotic replacement of the heart muscle as predisposing factors for syncope and sudden death in patients with AS. The sudden death of 2 of 17 patients with ventricular tachycardia in this study and the high incidence of sudden death reported by others add strong support to the thesis that ventricular tachyarrhythmias play a significant role in determining the eventual mortality rate. Since most patients are surgical candidates, a prospective study to answer this question adequately is impossible. Seven patients had bundle branch block, but no bradycardias were observed as another possible mechanism of sudden death.

Methodologic problems: The main point of criticism against the grading system for ventricular arrhythmias[9] is that a person can be assigned only to 1 grade and that the frequency of VPB is not taken into account in the higher grades 3 to 4B. To overcome these problems, we evaluated the recordings with respect to (1) number of VPB, and (2) the grade of arrhythmias. All grades of arrhythmia detected in each patient were listed. Thus, the total number of patients is >93 and the total percentage is >100% in Table III. Both a high incidence of VPB and a high grade of ventricular arrhythmia may identify patients with reduced left ventricular function, confirming that a higher grade of arrhythmia is usually associated with a higher incidence of VPB.

Variations in the frequency of uniform and complex ventricular arrhythmias are well documented.[26,27] Only 3 of 12 patients with 2 consecutive 24-hour recordings remained in the same grade of arrhythmia (Table I). This is mainly due to the low frequency of paired VPB and ventricular tachycardia, which were detected only once or twice in some patients during 24 hours. It is surprising that only 1 of 12 patients with 2 recordings changed from grade 0 to 2 to grade 3 to 4B. Thus, the separation of patients in grades 0 to 2 and grades 3 to 4B according to the results of ambulatory monitoring appears to be sufficiently stable. As demonstrated in Figure 2, these 2 classifications of arrhythmia best separate patients with normal and reduced left ventricular function in daily routine monitoring. However, the considerable overlap, also shown in Figure 2, has to be taken into account.

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Left Ventricular Response to Isometric Exercise and Its Value in Predicting the Change in Ventricular Function After Mitral Valve Replacement for Mitral Regurgitation

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Reduced left ventricular (LV) afterload and its effect on the resting ejection fraction may lead to overestimation of LV function in mitral regurgitation (MR). To evaluate LV function during increased afterload of the heart, an isometric handgrip test was performed during cardiac catheterization in 15 patients with mitral regurgitation (MR group) and in 9 normal subjects (normal group). Twelve months after successful mitral valve replacement (MVR) the patients were recatheterized, and the value of preoperative stress testing in predicting the change in resting ventricular function after surgery was estimated.

Isometric exercise caused an increase in end-systolic wall stress, a measure of ventricular afterload, in both the MR group and the control group ($p < 0.001$). The ejection fraction remained unchanged in the control group, but decreased from 0.58 ± 0.08 to 0.53 ± 0.08 in the MR group ($p < 0.001$). After MVR, end-systolic wall stress increased significantly ($p < 0.001$) and the ejection fraction decreased from 0.58 ± 0.05 to 0.51 ± 0.1 ($p < 0.05$). A positive correlation existed between the change in the ejection fraction during preoperative stress testing and the change in the resting ejection fraction after MVR ($r = 0.65$, $p < 0.01$). In 8 patients whose resting ejection fraction was within normal limits (>0.55) preoperatively, the ejection fraction was depressed (<0.55) 1 year after surgery. In all but 1 of these patients the isometric exercise revealed the reduced ventricular response to afterload stress preoperatively (decrease of the ejection fraction >0.03 during exercise). Therefore, the isometric exercise-induced change in LV function appears to predict the influence of MVR on LV function.

The ejection fraction is used to quantitate left ventricular (LV) function in patients with heart disease. However, it may lead to overestimation of myocardial function in patients with mitral regurgitation (MR).[1] The regurgitant mitral valve reduces LV afterload, allowing a greater part of the contractile force of the heart to be expended in shortening myocardial fibers than in developing tension.[2,3] The systolic unloading often leads to a normal ejection fraction despite myocardial dysfunction. The imposition of a competent mitral valve increases ventricular afterload and results in a decrease in the ejection fraction.[4–6]

Isometric exercise increases the afterload of the heart and is useful as a stress test.[7–9] The purpose of our study was to evaluate by invasive methods whether isometric exercise could unmask LV dysfunction in patients with MR. Second, we aimed to examine the value of an afterload stress test in predicting the influence of mitral valve replacement (MVR) on ventricular function.

Methods

Fifteen patients with moderate or severe MR (3+/4 or 4+/4 MR on LV cineangiography) and 9 normal subjects participated in the study. The patients were studied by cardiac catheterization preoperatively and 12 months after MVR. Patients with concomitant aortic valve disease (>10 mm Hg systolic gradient across aortic valve or clinical signs of aortic regurgitation, or both) were excluded. Patients with significant mitral stenosis (mitral valve area <2.0 cm^2) were also excluded. No regional wall abnormalities were seen on cineangiography in patients with MR. Five normal subjects underwent cardiac catheterization because of chest pain and 4 because of suspected intracardiac shunt. They were considered normal because the ejection fraction was >0.60, they showed no regional abnormalities in wall motion on cineangiography, LV end-diastolic pressure was ≤13 mm Hg, and

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TABLE I Hemodynamic Data at Rest and During Isometric Exercise

	HR (beats/min)		LVPSP (mm Hg)		LVEDP (mm Hg)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
			MR Group			
1	83	115	104	126	12	12
2	80	171	135	155	20	11
3	72	77	91	101	15	19
4	74	78	109	138	12	10
5	77	80	122	128	20	21
6	68	113	122	124	19	18
7	52	65	108	125	13	15
8	109	125	105	124	12	12
9	69	125	115	141	10	12
10	82	92	113	126	26	26
11	85	95	121	151	36	34
12	69	80	144	162	13	11
13	80	86	138	143	14	15
14	85	100	111	133	17	20
15	70	72	161	165	13	13
Mean ± SD	77 ± 12	100 ± 26	120 ± 18	136 ± 17	17 ± 7	17 ± 7
p value	<0.005		<0.001		NS	
			Control Group			
1	74	92	152	184	4	6
2	77	84	130	141	12	13
3	75	85	136	140	12	11
4	78	127	143	169	6	3
5	88	103	117	142	8	8
6	76	93	153	172	11	10
7	63	68	125	158	12	12
8	73	115	133	165	14	14
9	68	75	131	146	12	12
Mean ± SD	75 ± 7	94 ± 19	135 ± 12	157 ± 16	10 ± 3	10 ± 4
p	<0.01		<0.001		NS	

p values determined with paired *t* test.
HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; SD = standard deviation.

they had no coronary disease, intracardiac shunt, or valve lesion.

The mean age of the MR group was 50 ± 5 years and consisted of 7 women and 8 men. The mean age of the control group was 40 ± 11 years and consisted of 5 women and 4 men. Ten patients in the MR group had atrial fibrillation in both pre- and postoperative studies; other 5 patients and all normal subjects were in sinus rhythm. Ten patients had chronic MR, which was considered the result of rheumatic fever; 3 patients had ruptured chordae tendineae; and 2 patients were considered to have a "floppy" mitral valve. All patients in the MR group were receiving digitalis and diuretic therapy during pre- and postoperative studies. No patient was receiving beta-blocking or vasodilating agents. In 11 patients the valve was replaced by a Björk-Shiley disc valve prosthesis and in 4 patients by a St Jude's medical valve prosthesis.

Pre- and postoperative invasive studies: Pre- and postoperative right- and left-sided cardiac catheterization was performed through the cubital vein and the brachial artery. Right atrial, pulmonary, and pulmonary capillary wedge pressure was recorded with a Statham P23Ia transducer. Left ventricular pressure was recorded with a high-fidelity Millar tip-transducer. Its pressures were matched against fluid-filled luminal pressures. A data acquisition system (Hewlett-Packard 5600B) was used for the standard recording of pressure. Selective biplane LV cineangiography was performed in the 45° right anterior oblique position. In normal subjects with chest pain, coronary angiography was performed by the Judkins technique. In the MR group neither coronary angiography nor coronary bypass surgery was performed.

Isometric exercise tests: After preoperative ventriculography, LV pressure was recorded until a return to baseline levels. Thereafter, at least 20 minutes after resting cineangiography, the patients were asked to perform a handgrip test. Each patient's maximal voluntary handgrip contraction was determined as the average of 2 or 3 maximal attempts using a hand dynamometer (Martin, Germany) held in the left hand. After calculation of the maximal voluntary contraction, the patients were asked to perform a sustained handgrip of 30% of the mean maximal voluntary contraction. The patients were watched carefully to avoid the Valsalva maneuver. During sustained grip, LV pressure, heart rate, and cardiac output by thermodilution were determined every minute for 4 minutes. After 4 minutes of handgrip and with the patients still performing the grip, LV cineangiography was again performed.

Measurements: Left ventricular volumes were measured from 1 or 2 representative beats and the postextrasystolic beats were discarded. The rate of filming was 50 frames/s. The volume curve was obtained by tracing each frame throughout 1 or 2 cardiac cycles. In patients with atrial fibrillation, the volume measurements were taken on beats that most closely approximated the average R-R interval for the basal ventricular response. In postoperative angiograms the cycle length was chosen for analysis, which mostly resembled that of the preoperative cycle. The greatest individual variation in R-R cycle lengths in pre- and postoperative volume measurements was 0.14 second. The contours of the left ventricle were digitized at biplane with a sonic pen on the projection screen using the Hewlett-Packard 5600B and the biplane area-length method for volume.[10] Regression equations previously established in our laboratory were used.[11] The LV pressure curve was recorded simultaneously with the angiogram at a paper speed of 150 mm/s. The mitral valve area was calculated

TABLE II Preoperative Angiographic Data at Rest and During Exercise

	ESVI (ml/m²)		EDVI (ml/m²)		ESWS (g/m²)		ESWS/ESVI		EF (%)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
					MR Group					
1	61	80	159	176	140	165	2.3	2.1	62	58
2	94	96	170	151	145	180	1.6	1.9	45	36
3	86	93	198	199	190	210	2.2	2.3	57	53
4	61	68	238	198	120	215	2.0	3.2	74	66
5	57	80	151	162	120	155	2.1	1.9	62	51
6	77	81	153	140	160	190	2.1	2.3	50	43
7	42	45	95	95	145	180	3.5	3.9	56	53
8	42	38	94	94	195	210	4.7	5.5	55	56
9	45	37	90	90	185	230	4.1	6.2	49	49
10	52	54	162	162	250	240	4.8	4.4	68	65
11	60	61	143	143	150	285	2.5	3.0	58	57
12	47	52	103	103	165	210	3.6	4.0	55	48
13	24	34	68	68	160	190	6.7	5.6	64	56
14	77	74	156	151	100	125	1.3	1.6	51	51
15	25	28	79	68	150	170	5.9	6.1	69	58
Mean ± SD	57 ± 20	61 ± 22	137 ± 44	133 ± 44	158 ± 37	197 ± 39	3.3 ± 1.6	3.6 ± 1.6	58 ± 8	53 ± 8
p value	<0.05		NS		<0.001		NS		<0.001	
					Control Group					
1	27	19	85	84	215	240	7.9	12.8	72	78
2	31	31	104	94	280	295	9.0	9.8	71	67
3	16	15	64	74	190	210	11.8	14.0	78	79
4	18	19	78	81	270	285	15.0	15.0	77	77
5	19	20	57	62	200	240	10.5	12.0	66	65
6	15	15	54	56	210	225	14.0	15.0	71	73
7	17	19	59	62	240	250	14.1	13.2	72	69
8	24	25	62	69	170	200	7.1	8.0	63	62
9	20	18	68	59	235	260	11.1	14.4	73	73
Mean ± SD	21 ± 5	20 ± 5	70 ± 16	71 ± 13	225 ± 35	245 ± 30	11.2 ± 2.8	12.7 ± 2.7	71 ± 5	71 ± 6
p	NS		NS		<0.001		<0.05		NS	

p values determined with paired *t* test.
EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; ESWS = end-systolic wall stress.

from Gorlin's modified formula as described by Hammermeister et al.[12] The flow of the orifice was measured from the total LV stroke volume. The LV mass was calculated as described by Rackley et al.[13] The mitral regurgitant fraction was measured by subtracting the stroke volume, determined by the Fick method and by thermodilution during exercise, from the total LV stroke volume. Circumferential wall stress was estimated from the following formula:[14] $(PR_i/H)(a_h)[1 - 1/2(R_i/B)]^2$, where p = LV pressure, R_i = minor semiaxis, B = major semiaxis, H = wall thickness, and $a_h = (r_m + H/2)$, $r_m = B^2/R_i$. End-systolic wall stress was estimated by measuring the pressure, minor and major semiaxes, and the wall thickness at end-systole. End-systole was determined at the point where volume was at a minimum and wall thickness at a maximum. Volume and wall thickness were determined at 20-ms intervals throughout 1 or 2 cardiac cycles by tracing each frame.

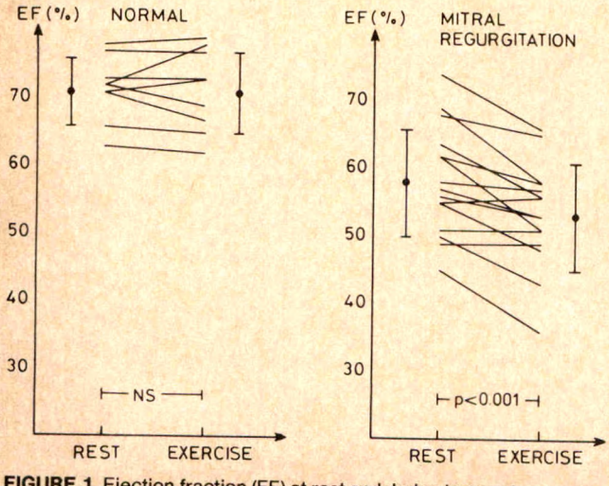

FIGURE 1. Ejection fraction (EF) at rest and during isometric exercise in normal subjects and in patients with mitral regurgitation.

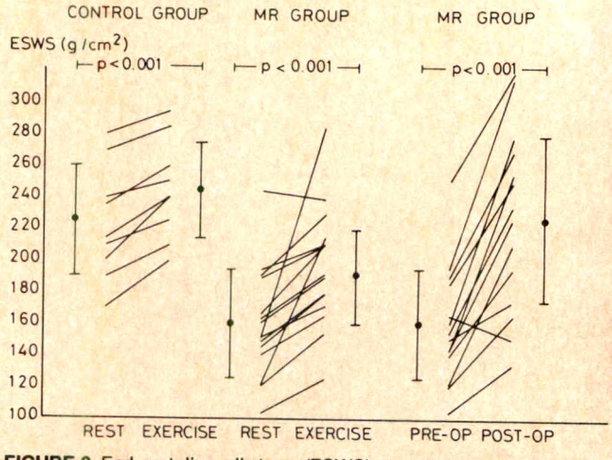

FIGURE 2. End-systolic wall stress (ESWS) at rest and during isometric exercise in normal subjects and in patients with mitral regurgitation. **Right panel** presents the change in the end-systolic wall stress after mitral valve replacement. PRE-OP = preoperative; POST-OP = postoperatively.

TABLE III Pre- and Postoperative Resting Angiographic Data

	ESVI (ml/m²)		EDVI (ml/m²)		EF (%)		ESWS/ESVI	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	61	97	159	154	62	37	2.3	2.0
2	94	65	170	125	45	48	1.6	3.8
3	86	44	198	93	57	53	2.2	3.1
4	61	47	238	100	74	53	2.0	4.2
5	57	54	151	105	62	49	2.1	3.1
6	77	92	153	133	50	31	2.1	2.7
7	42	27	95	73	56	64	3.5	8.1
8	42	27	94	75	55	64	4.7	8.1
9	45	47	90	106	49	56	4.1	5.3
10	52	21	162	69	68	70	4.8	10.7
11	60	66	143	137	58	52	2.5	3.0
12	47	49	103	94	55	48	3.6	3.1
13	24	46	68	80	64	43	6.7	5.0
14	77	54	156	111	51	52	1.3	2.1
15	25	37	79	65	69	44	5.9	4.6
Mean ± SD	57 ± 20	52 ± 22	137 ± 48	101 ± 27	58 ± 8	51 ± 10	3.3 ± 1.6	4.5 ± 2.5
p	NS		<0.001		<0.05		<0.05	

p values determined with paired *t* test.
EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; ESWS = end-systolic wall stress; SD = standard deviation.

Calculations: Statistical analysis was performed using the paired *t* test in comparing individual data at rest with data during exercise and by comparing individual changes between pre- and postoperative data. The standard *t* test was used to compare changes in different groups. A standard correlation coefficient was used in estimating correlations.

Results

Clinical data: Preoperatively, 4 patients were in functional class IV, 10 in class III, and 1 in class II. No patient had a history of angina pectoris. The mean duration of symptoms was 53 ± 37 months. The mean mitral regurgitant fraction was 0.47 ± 0.13. After MVR all patients showed functional improvement; 11 patients were in class II and 4 in class I.

Preoperative hemodynamic and angiographic data at rest and during isometric exercise: Individual hemodynamic data at rest and during exercise in both the MR and the control group are presented in Table I. Heart rate and LV peak systolic pressure increased significantly in both groups, but the end-diastolic pressure remained unchanged during exercise.

Individual preoperative angiographic data at rest and during exercise are presented in Table II. The end-systolic volume increased in the MR group but remained unchanged in the control group. The end-diastolic volume remained unchanged in both groups during exercise. The ejection fraction decreased significantly in the MR group while remaining unchanged in the control group (Fig. 1). End-systolic wall stress increased significantly in both groups during handgrip exercise (Fig. 2). End-systolic wall stress/end-systolic volume index ratio remained unchanged in the MR group whereas it increased significantly in the control group during exercise. The mitral regurgitant fraction increased moderately but not significantly during exercise (0.47 ± 0.13 at rest, 0.53 ± 0.18 during exercise; difference not significant [NS]).

Pre- and postoperative hemodynamic and angiographic data: Individual angiographic data pre- and postoperatively are presented in Table III. End-systolic volume remained unchanged, but end-diastolic volume decreased significantly after surgery. The ejection fraction decreased (Fig. 3), but the end-systolic wall stress/end-systolic volume index ratio increased after MVR. End-systolic wall stress increased from 159 ± 36 to 223 ± 67 g/m² ($p < 0.001$) after MVR. The LV mass index decreased from 130 ± 47 to 111 ± 35 g/m² ($p < 0.05$). Mean pulmonary artery pressure decreased from 33 ± 13 to 22 ± 6 mm Hg ($p < 0.005$) and mean pulmonary capillary wedge pressure from 22 ± 5 to 13 ± 3 mm Hg ($p < 0.001$) after surgery. The cardiac index remained unchanged (3.0 liters/m² preoperatively, 2.9 postoperatively; NS).

Correlations between pre- and postoperative measures of LV function: There was no correlation between pre- and postoperative resting ejection fraction ($r = 0.11$, NS) or between preoperative ejection fraction and postoperative end-systolic wall stress/end-systolic volume index ratio ($r = 0.23$, NS). The preoperative

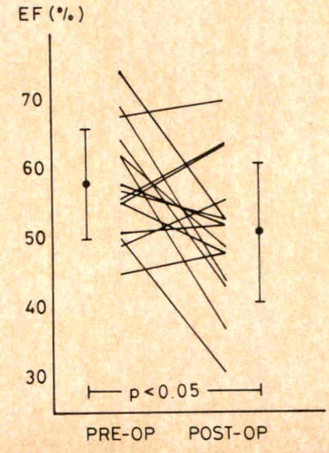

FIGURE 3. Preoperative (PRE-OP) and postoperative (POST-OP) ejection fraction (EF) in patients with mitral regurgitation.

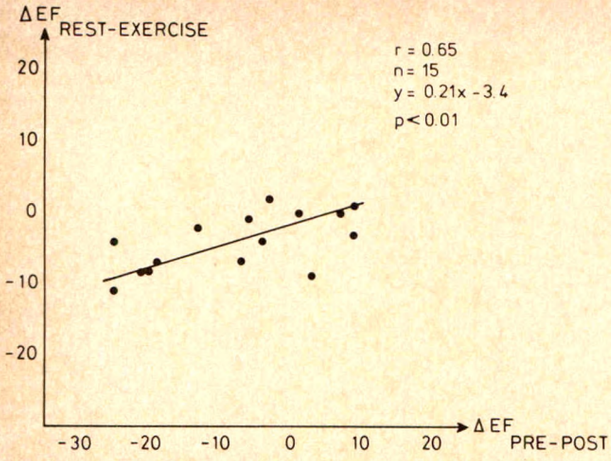

FIGURE 4. Correlation between the change in ejection fraction in percent units during isometric exercise test ($\Delta EF_{REST-EXERCISE}$) and the change in EF in percent units after mitral valve replacement ($\Delta EF_{PRE-POST}$).

resting ratio between end-systolic wall stress and end-systolic volume index did not correlate with the postoperative resting ejection fraction (r = 0.37, NS). However, a correlation existed between the resting pre- and postoperative end-systolic wall stress/end-systolic volume ratio (r = 0.56, p <0.05). The change in the ejection fraction during exercise correlated well with the change in the resting ejection fraction after surgery (r = 0.65, p <0.01) (Fig. 4) and even better with the change in the resting end-systolic wall stress/end-systolic volume index ratio after surgery (r = 0.75, p <0.001). The correlation between the preoperative resting ejection fraction and the preoperative resting ratio between end-systolic wall stress/end-systolic volume index was poor (r = 0.43, NS). However, after MVR the resting ejection fraction and the resting end-systolic wall stress/end-systolic volume index ratio correlated well with each other (r = 0.78, p <0.001). In 8 patients whose ejection fraction preoperatively was within the normal limits (>0.55), the ejection fraction decreased below 0.55 after surgery. In all but 1 of these patients the ejection fraction decreased >3 percent units during isometric exercise preoperatively, revealing the reduced ventricular response to afterload stress. In 4 patients the end-systolic wall stress/end-systolic volume index ratio decreased after surgery. In these 4 patients the ejection fraction also decreased significantly during isometric exercise preoperatively (>3 percent units).

Discussion

Isometric handgrip exercise has been used to evaluate LV functional reserves in various cardiovascular disorders.[7–9] In the present study we evaluated the ventricular response to isometric exercise in patients with MR and in normal subjects. The theoretical basis for using handgrip exercise as a stress test was the fact that systolic afterload is reduced in MR.[2,3] Increasing the systolic load of the left ventricle by handgrip exercise might reveal latent LV dysfunction and might also simulate the effect of a competent mitral valve prosthesis on ventricular afterload.

Ventricular response to isometric exercise in normal subjects and in patients with MR: The end-systolic volume and the ejection fraction remained unchanged during the afterload stress caused by exercise in normal subjects, indicating increased contractility of the left ventricle in the normal heart. Augmentation of systolic ventricular function during isometric exercise in normal subjects has also been demonstrated in previous studies.[15,16] In most patients with MR the exercise resulted in an increase in end-systolic volume and a decrease in ejection fraction. The increased heart rate probably caused the end-diastolic volume to remain unchanged; otherwise, the afterload stress might have increased the mitral regurgitant fraction and the preload of the left ventricle.

Isometric exercise unmasked the depressed systolic function in many patients with a normal ejection fraction at rest. Previous studies have shown that the resting ejection fraction may remain normal despite depressed myocardial contractility in MR.[1] The lack of correlation between the resting ejection fraction and the resting end-systolic wall stress/end-systolic volume index ratio, which is nearly independent of the loading conditions of the heart,[17] suggests that the ejection fraction at rest may be an invalid index in quantitating the ventricular function in MR.

Correlation between the change in ventricular function during exercise and that after surgery: Of clinical interest was the finding that the change in ejection fraction during the preoperative afterload stress predicted the change in ventricular function after MVR. The decrease in ejection fraction during preoperative exercise test was mainly due to the increase in end-systolic volume. The decrease in ejection fraction after surgery depended mainly on the decrease in end-diastolic volume without a concomitant decrease in end-systolic volume. In other volume overload states, as in aortic regurgitation, in which ventricular afterload is not significantly reduced preoperatively, the abolition of volume overloading results in a decrease in both end-diastolic and end-systolic volume.[18] In patients with MR, despite abolition of volume overloading, the increased afterload caused by the mitral valve[19] results in unchanged end-systolic volume. Our data indicate that acute afterload stress makes it possible to predict the degree to which the myocardium is able to tolerate the long-term influence of afterload stress caused by MVR.

The end-systolic wall stress/end-systolic volume index ratio, which was recently shown to predict the clinical outcome after MVR,[20] had some predictive value also in terms of postoperative ventricular function. The ratio of end-systolic wall stress/end-systolic volume index may also depend on the duration and extent of the valvular lesion, not only on myocardial function. The reliable quantitation of this ratio requires highly invasive methods and is not suitable for serial preoperative measurements. The LV response to isometric exercise can easily be quantitated also by noninvasive methods, such as echocardiography[21] and radionuclide

angiography,[22] and so offers the possibility of monitoring the ventricular response to afterload stress.

Possible methodologic limitations of the study: Atrial fibrillation may affect quantitation of the ventricular volumes and the ejection fraction. As the individual cycle-length was chosen as equal as possible in pre- and postoperative angiograms, we do not think that cycle-length variation was of major significance in the results. The variations in determining the end-systolic point may affect the estimation of the end-systolic wall stress, as the pressure curve declines rapidly near end-systole in MR. We tried to eliminate the possible variation in determining the end-systole by measuring volumes and wall thickness at 20-ms intervals; moreover, as we had simultaneous pressure recordings with the angiogram, we do not believe that the changes seen in end-systolic wall stress during exercise and after surgery were due to variations in the end-systolic point. Finally, we did not perform coronary arteriography in patients with MR. Because ischemic heart disease is not exceptionally common in patients with MR[3] and because no patient had angina pectoris, we do not think that the reduced ventricular response to exercise was due to coronary artery disease.

Implications: All of our patients had functional improvement after surgery. Therefore, our results do not provide data on the value of preoperative isometric exercise testing in predicting the postoperative clinical outcome. However, evaluation of the LV response to isometric exercise can predict changes in ventricular function after surgery and thus may provide information helpful in making therapeutic decisions regarding valve replacement in patients with MR.

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Preoperative Invasive Testing in Mitral Stenosis: Indications Based on Assessment of Diagnostic Yield

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The role of preoperative invasive testing in mitral stenosis was assessed in 82 patients undergoing cardiac catheterization for isolated mitral stenosis. The patients were diagnosed by physical examination and echocardiography and were considered for surgical treatment primarily to relieve dyspnea. They had no precordial murmur attributable to an aortic valvular lesion and had no history of chest pain. The presence of mitral stenosis was confirmed at catheterization in all patients. All 38 patients in New York Heart Association functional class III and 8 of 9 patients in class IV had hemodynamic confirmation of mitral disease warranting operation. Although a mitral gradient was present in all 35 patients in class II, operation was not recommended in 9 (26%) of 35 with normal or mildly elevated pulmonary arterial wedge pressure. Invasive testing did not increase preoperative knowledge of aortic, tricuspid, or pulmonary valvular lesions which required surgical treatment. Coronary arteriography was performed in 44 patients (54%) and identified 4 patients with luminal narrowing (>70% diameter reduction) affecting 1 or 2 arteries. These results suggest that preoperative invasive testing in patients with mitral stenosis is unnecessary when symptoms are moderate to severe and clinical evidence of aortic valvular or coronary artery disease is absent. However, preoperative cardiac catheterization is indicated in patients with mild symptoms to avoid unnecessary or premature mitral valve operations.

The risk and rising cost of cardiac catheterization, at a time of improvements in noninvasive imaging, have prompted reconsideration of the need to use invasive tests to evaluate patients with valvular heart disease. Clinical course and short-term survival after valve replacement have been similar whether or not preoperative cardiac catheterization was performed.[1] Thus, editorial recommendations against routine invasive study have been made.[2,3] However, analysis of outcome only in patients undergoing surgical treatment may not identify patients with hemodynamically insignificant disease whose operations were unnecessary or premature. Such operations may be avoided by routine cardiac catheterization of operative candidates. Invasive testing may additionally serve to assess operative risk and has been advocated for the detection of asymptomatic coronary artery disease.[4] Moreover, because of different clinical profiles in patients with different types of valvular lesions, global generalizations about indications for invasive diagnostic evaluations may not be valid.

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We examined in detail the role of cardiac catheterization in patients with mitral stenosis (MS) because of the relatively distinct and specific clinical and echocardiographic features of this disease. Other investigators[5] have specifically questioned the need for invasive procedures in MS. A small prospective study of decision-making in patients with MS suggested that management decisions based on clinical and noninvasive findings are not altered by subsequent invasive testing.[6] In patients with MS considered candidates for mitral operation, we report the results of routine preoperative cardiac catheterization and the extent to which these results contribute to clinical management.

Methods

A total of 167 consecutive patients undergoing echocardiographic and invasive evaluation of suspected MS between March 1974 and July 1981 at Stanford Medical Center were retrospectively identified using a computer-based data bank. During this period, no patients evaluated by the Stanford cardiology service had surgical treatment for MS without preceding cardiac catheterization. Five patients who were considered operative candidates primarily for treatment of arrhythmia or recurrent embolization were excluded. Before invasive testing, all patients in the study were considered candidates for mitral valve operation primarily for relief of

dyspnea and were assigned to New York Heart Association functional class II, III, or IV (class II, symptoms with ordinary activity; class III, symptoms with less than ordinary activity; class IV, symptoms at rest). All patients received physician interview, physical examination confirming the presence of a diastolic murmur suggestive of MS, electrocardiography, and chest roentgenography. Before cardiac catheterization, each had M-mode echocardiography confirming the presence of a rheumatic mitral valve. Two-dimensional echocardiography was performed during the last 31 months of the 84-month study period.

One hundred sixty-two operative candidates with MS were identified by the foregoing criteria. Additional criteria were then applied to distinguish patients with relatively isolated mitral disease from those with clinical evidence of other lesions with potential surgical implications (Fig. 1). The 80 patients with other clinically evident lesions included 9 patients with suspected aortic stenosis (any basilar systolic ejection murmur of suspected aortic valve origin), 32 with suspected aortic regurgitation (any diastolic decrescendo murmur attributed to aortic regurgitation), 22 with both suspected aortic stenosis and regurgitation, 2 with prosthetic aortic valves, 3 with a history of angina pectoris, 3 with suspected aortic valvular disease and angina pectoris, 5 with previous myocardial infarction, and single patients with a mitral Carpentier ring, suspected tricuspid stenosis, previously diagnosed alcoholic cardiomyopathy, and suspected subclavian steal syndrome. These patients with aortic valvular disease, coronary artery disease, or less common conditions were excluded from further study. The study group was composed of the remaining 82 patients with clinical and echocardiographic features of MS and included patients with associated mitral, pulmonary, or tricuspid regurgitation.

Cardiac catheterization included hemodynamic measurements during exercise if resting pulmonary artery and pulmonary arterial wedge pressures were normal or mildly elevated. Mitral valve area was determined by the Gorlin formula using Fick cardiac output. The computed mitral valve area was recognized as underestimated in moderate or severe mitral regurgitation. Left ventricular angiography was performed in all except 1 individual. All patients had no clinical evidence of coronary artery disease. Because this study covered a broad time span, coronary arteriography was not performed with a consistent age criterion but was obtained in 54% of patients.

The 82 study patients were characterized by age, sex, severity of symptoms, history of previous commissurotomy, clinically evident mitral regurgitation, ancillary echocardiographic findings, results of cardiac catheterization and angiography, final therapeutic decisions, and in-hospital operative mortality. Patients with evidence of moderate to severe mitral regurgitation before catheterization were retrospectively identified by the presence of an apical holosystolic murmur of greater than grade 1 intensity (scale of 6) and at least 2 of 3 other criteria: left ventricular enlargement on precordial examination, left ventricular hypertrophy on electrocardiography without concomitant systemic hypertension, and diastolic left ventricular internal dimension >5.7 cm on M-mode echocardiography.

Results

Fourteen men and 68 women comprised the study group. Patients ranged in age from 21 to 75 years, with 77% between the ages of 40 and 70. Twenty-three pa-

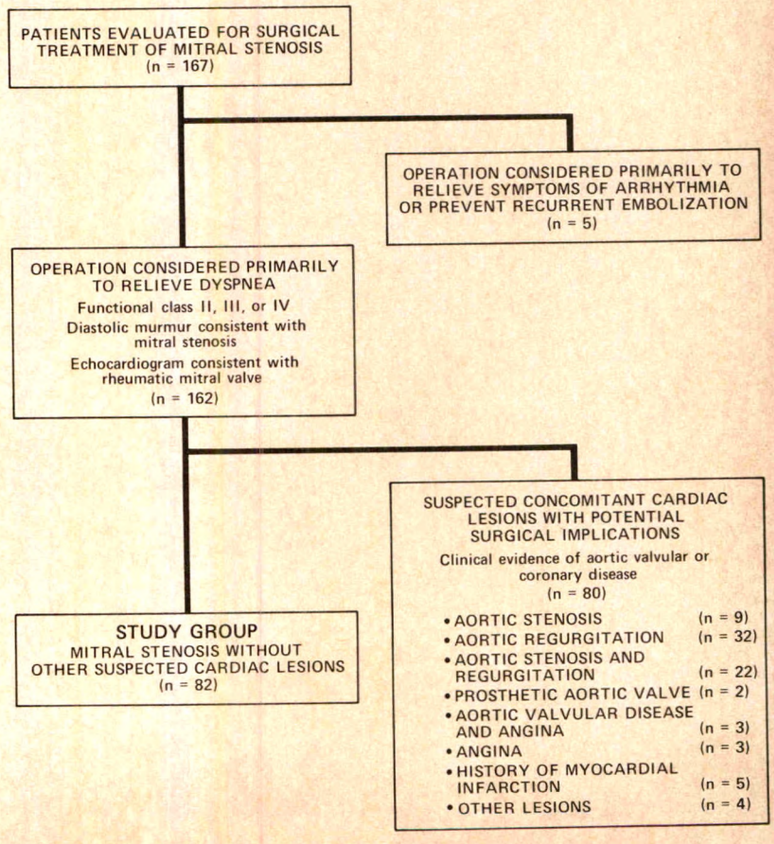

FIGURE 1. Diagram of study group selection among all patients considered for surgical treatment of mitral stenosis. Reasons for inclusion or exclusion are depicted with the number of patients in each category. The study group included cases of clinically evident mitral, pulmonary, and tricuspid regurgitation. Criteria for suspicion of aortic valvular disease are described in the text.

tients had mitral commissurotomy 2 to 24 years before reevaluation.

Of the 82 patients, 10 fulfilled the clinical criteria for moderate to severe mitral regurgitation. Five of these had moderate to severe mitral regurgitation by angiography (grade 3 to 4 on a scale of 4), and in 5 it was mild or absent. An additional 5 patients who did not meet the clinical criteria displayed moderate to severe mitral regurgitation angiographically. Confirmation or exclusion of high-grade mitral regurgitation by angiography did not alter subsequent management, as all of these patients had mitral valve replacement irrespective of the degree of mitral regurgitation. Because patients with high-grade mitral regurgitation all had mitral operations and could not reliably be distinguished clinically from patients with predominant valvular stenosis, all patients were grouped together for further analysis.

Figure 2 depicts the relation of severity of symptoms, calculated mitral valve area, and the final decision for or against surgical treatment. Eighty-nine percent of patients were in New York Heart Association functional class II or III. Although MS was confirmed in all patients, the calculated mitral valve area showed a wide range within each class and overlap between classes. All 38 patients in class III and 8 of 9 patients in class IV had mitral valve disease judged to be hemodynamically significant at catheterization and to warrant operation. The ninth patient in class IV had mild hemodynamic abnormalities disproportionate to the clinical classification, and surgery was not recommended. This patient complained of general fatigue as well as dyspnea, and a cardiac or pulmonary basis for the degree of disability could not be identified. One of the other 8 patients in class IV did not receive a final recommendation for surgical treatment because of poor left ventricular function, as will be discussed.

Ten patients with findings of mild mitral disease on cardiac catheterization were not referred for operation. Five of these had previous commissurotomy. The calculated mitral valve area was <1.5 cm^2 (range 0.8 to 1.4) in 5 of the 10 patients and ≥ 1.5 cm^2 (range 1.5 to 1.9) in 5. One of the 10 patients was in class IV and had a resting pulmonary arterial wedge pressure of 15 mm Hg. The other 9 patients were in class II and comprised 26% of the 35 class II patients. These 9 patients had resting pulmonary arterial wedge pressure <14 mm Hg (range 8 to 13) with an increase to ≤ 25 mm Hg (range 13 to 25) during exercise. Their pulmonary vascular resistance was <200 dynes·s·cm^{-5}. Of the remaining 26 patients in class II, who were advised to have a mitral operation, 8 had resting pulmonary arterial wedge pressure <14 mm Hg (range 11 to 13) which increased with exercise to ≥ 22 mm Hg (range 22 to 34).

Surgical treatment was recommended in 71 patients, and 69 patients had mitral operations. Mitral valve replacement with a porcine heterograft bioprosthesis was performed in 65 patients and mitral commissurotomy in 4. Two other patients decided not to undergo recommended operations. Six patients with minimal mitral calcification and low-grade mitral regurgitation on angiography were regarded as candidates for commissurotomy. However, final decisions between commissurotomy and valve replacement were made after direct intraoperative inspection of the mitral apparatus, leading to valve replacement in 2 of these patients.

Tricuspid regurgitation was clinically suspected in 7 patients and hemodynamically confirmed in 6. No other cases of moderate or severe tricuspid regurgitation were discovered on catheterization. Intraoperative assessment led to tricuspid operations in 4 of these pa-

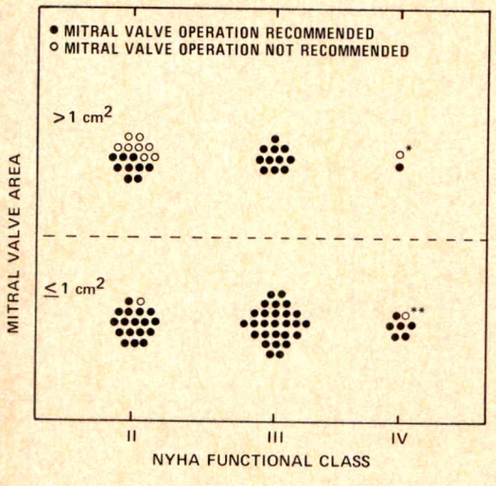

FIGURE 2. Relation of symptom severity by New York Heart Association (NYHA) functional classification, calculated mitral valve area, and final decision for or against surgical treatment of mitral stenosis. **Closed circles** represent patients who received a recommendation for operation; **open circles** represent patients who did not receive a recommendation for operation. For 1 patient (**) in class IV, surgical treatment was precluded by severe left ventricular dysfunction. Other patients who did not receive a recommendation for operation had normal or mildly elevated pulmonary arterial wedge pressure, including 1 patient (*) in class IV with a mitral valve area of 1.6 cm^2 and a resting pulmonary arterial wedge pressure of 15 mm Hg.

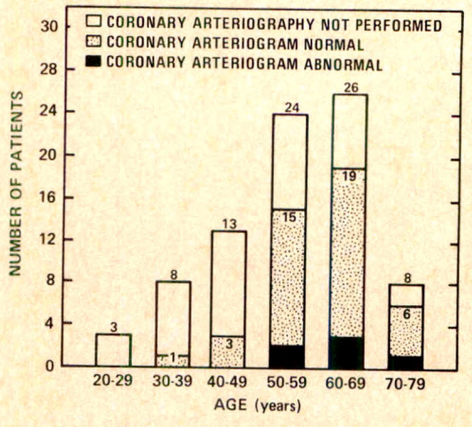

FIGURE 3. Age distribution by decade of patients with mitral stenosis who had cardiac catheterization. Total number of patients in each decade are indicated **above columns**; number of patients who had arteriograms are indicated within **shaded areas. Lightly shaded areas** represent patients who had coronary arteriograms that showed normal vessels or minimal stenoses of <50%; **darkly shaded areas** represent patients who had coronary arteriograms showing stenoses >50%.

tients; 3 underwent tricuspid anuloplasty and 1 received a tricuspid prosthesis for unsuspected primary rheumatic tricuspid disease.

Mild aortic stenosis was discovered at catheterization in 3 patients with peak aortic valve gradients of 17, 22, and 23 mm Hg. Concomitant aortic valve operations were not recommended. Severe pulmonary regurgitation suspected in 1 patient before catheterization was confirmed angiographically, but pulmonary valve surgery was not performed. Pulmonary vascular resistance was elevated above 400 dynes·s·cm^{-5} in 12 patients, but this finding did not alter the decision to operate.

Left ventricular ejection fractions <40% were noted in 4 patients. Those with ejection fractions of 32, 35, and 36% had mitral operations. Operation was not advised for 1 class IV patient with an ejection fraction <20%, for whom surgical risk was judged prohibitively high. Before catheterization, the echocardiogram in this patient showed left ventricular enlargement (left ventricular internal diastolic dimension 6.8 cm) with fractional shortening of 16%.

Coronary arteriography was performed in 44 of the 82 study patients (54%) and most frequently in patients >50 years of age (Fig. 3). Seven of 14 men and 37 of 68 women had arteriography. Thirty-four patients had entirely normal coronary arteries, whereas 4 others had minimal luminal narrowings <50% in major vessels. No left main coronary artery lesions were detected. Stenoses >50% were detected in the remaining 6 patients who ranged in age from 58 to 72 years and comprised 14% of the patients having arteriography. Two patients had moderate stenoses of 55 and 60%, the latter having aortocoronary bypass at mitral surgery. Severe stenoses were detected in 4 patients, comprising 9% of those having arteriography. Of 3 patients with a single stenosis >90%, 2 had coronary bypass during the mitral operation. One patient had 90% stenoses of 2 major vessels and received 2 grafts.

Complications of cardiac catheterization included pulmonary edema in 2 patients in New York Heart Association class III and transient bradycardia and hypotension in 1 patient. There were no fatalities as a direct result of the catheterization. The only hospital death occurred in a patient with moderate mitral regurgitation, normal ventricular function, and normal coronary anatomy preoperatively; this patient died in refractory ventricular failure after cardiopulmonary bypass.

Discussion

Our past practice of performing routine cardiac catheterization in all patients with suspected MS before operation provides an opportunity to examine the extent to which invasive testing contributes to clinical management. Potential contributions of invasive testing include discovery of hemodynamically insignificant disease, occult lesions requiring operative repair at the time of mitral operation, and factors associated with an inordinately high surgical risk.

M-mode echocardiography can confirm the presence of rheumatic mitral valvular disease qualitatively, but the severity of the lesion cannot be dependably predicted.[7] More recently, 2-dimensional echocardiographic measurement of the area of the stenotic mitral valve orifice has been shown to be accurate.[8–11] Because the dyspnea of MS is believed to be a consequence of elevated left atrial and pulmonary capillary pressure,[12] quantitation of the mitral valve area alone may not reflect the true hemodynamic substrate for a patient's symptoms. This is suggested by our catheterization data, which confirm a wide variation of symptoms for specified valve areas. Left atrial pressure elevation is determined by cardiac output and the extent of valvular stenosis, and cardiac output may differ widely between patients with similar valve areas. In some patients, coexisting abnormalities such as mitral regurgitation, ventricular dysfunction, or disproportionate pulmonary hypertension may also contribute to disability. Although the interval between the aortic component of the second heart sound and the mitral opening snap correlates with left atrial and pulmonary capillary pressure, this variable is not dependable enough to designate which patients have disease warranting operation.[13,14]

Ten patients hospitalized for possible mitral operation, but found to have normal or mildly elevated pulmonary arterial wedge pressure at rest and on exercise were not finally recommended for surgical treatment. All but 1 of these patients had symptoms of New York Heart Association functional class II. They did not have an elevated left ventricular diastolic pressure known to mask the hemodynamic findings of MS,[15] nor was their pulmonary vascular resistance substantially elevated. Mitral operation was recommended in 8 patients in class II with a normal or minimally elevated resting pulmonary arterial wedge pressure. These patients generally showed greater increases in pressure during exercise than did patients withheld from operation.

Cardiac catheterization results, most importantly the pulmonary arterial wedge pressure, affected management of these patients with class II symptoms. There was an overlap of hemodynamic values between the patients withheld from operation and those treated surgically, reflecting the fact that a final decision for or against surgical treatment is multifactorial, involving the patient's symptoms and the physician's subjective and objective evaluation. These factors may have contributed to the heterogeneity of management choices among patients with less severe disease. Although it can be proposed that the catheterization data were misleading and that all patients in the present series would still have benefited from surgical treatment, such benefit cannot be reasonably assumed if the hemodynamic measurements were accurate.

In contrast to patients in New York Heart Association functional class II, all patients in class III and all except 1 patient in class IV had findings at cardiac catheterization that confirmed the presence of mitral disease regarded as hemodynamically significant. This suggests that patients in functional classes III and IV can be managed effectively without invasive assessment of the mitral lesion. It is recognized that without invasive study a rare patient in class III or IV may undergo operation for hemodynamically mild mitral disease.

Among our patients in classes III and IV, 1 patient in class IV would have received a premature mitral operation if routine cardiac catheterization had not been performed.

The role of preoperative invasive testing in identifying candidates for mitral commissurotomy is minimal in this series, and only 4 commissurotomies were performed among 69 mitral procedures. The reason may be the older age of the patients and a tendency of the surgical staff at our institution to frequently favor valve replacement with a bioprosthesis. The condition of the mitral apparatus as assessed by direct intraoperative inspection is the final determinant of the type of mitral operation.

Ancillary findings at cardiac catheterization were infrequent and seldom altered surgical management in our series. Physical examination gave adequate evidence of tricuspid regurgitation, which was further assessed intraoperatively. Truly occult aortic valve disease was rare and not severe enough to require treatment in this group. Despite the clinical impression that severe pulmonary hypertension may portend a more prolonged postoperative requirement for mechanical ventilation, knowledge of the pulmonary vascular resistance, in practice, did not alter the decision for or against surgical treatment.

Left ventricular contractility is usually well preserved in patients with MS, although severe left ventricular dysfunction can occur when there is long-standing mitral regurgitation or an independent cardiomyopathy. Because there was only 1 such patient in our study group, routine invasive testing of all patients is not warranted in identifying this small minority. Furthermore, very poor ventricular function may often be suspected on clinical grounds or on echocardiography. Either this suspected subgroup or all patients could currently undergo quantitation of ventricular function by noninvasive imaging.

The occurrence of coronary artery disease in our patients with MS was small. This finding differs from the more common association of coronary artery disease with aortic stenosis.[16,17] The 3 single-vessel and the 1 double-vessel aortocoronary bypass operations performed in this group were of unknown benefit in the absence of chest pain or a history of myocardial infarction. It is unlikely that bypass of a single coronary artery improves long-term prognosis.[18–20] Moreover, randomized controlled studies of coronary artery bypass surgery have included only patients with symptomatic disease.[21,22] Aortocoronary bypass grafting has been advocated in patients difficult to wean from cardiopulmonary bypass after valve replacement.[4] However, the efficacy of this practice has not been demonstrated, and poor ventricular recovery is uncommon in cases of predominant MS.

Some potential limitations of our retrospective study can be noted. Patients may have been excluded from analysis if they were mistakenly not entered into the computer databank, although this is unlikely. The New York Heart Association functional classification used for our patients is partly subjective, not fully reproducible, and influenced by factors other than cardiac disease, yet reflects the symptoms that usually lead patients to evaluation for possible operation.

There was no distinct threshold of hemodynamic abnormality for recommending surgical treatment in class II patients. In practice, it may not be possible to form strict guidelines for these decisions. The decision-making process for our patients relied in part on standard hemodynamic and angiographic results which occasionally may be inaccurate or misleading.[15] Two-dimensional echocardiography is now a widely used technologic advancement that was unavailable during most of the study period; however, the utility of our observations is not altered because the valve area alone was not the primary determinant in recommending surgical treatment.

The appropriateness of surgical treatment can well be demonstrated by objective pre- and postoperative functional assessment, which is not available in this study. We have empirically taken the therapeutic decisions made in this patient group as the basis for evaluating the impact of information obtained at catheterization. Although management decisions are made by a diverse group of physicians, their therapeutic choices reflect a consensus of opinion with regard to the use of clinical and catheterization results.

We have examined the role of cardiac catheterization only in cases of clinically suspected MS with or without mitral, pulmonary, or tricuspid regurgitation. Our conclusions apply only to this subgroup of patients. Patients with primary symptoms of arrhythmia or embolus and patients with concurrently suspected aortic valvular or coronary disease were excluded because of potential surgical indications different from those in the study group.

Recent recommendations for the application of invasive testing in valvular heart disease vary widely and include both strong advocacy of and opposition to routine preoperative cardiac catheterization.[1–4] These editorial statements tend generally to address this issue broadly for patients with all types of valvular lesions. We believe that indications for or against invasive testing will need to be determined separately for specific types of valvular disease. We have assessed the contributions of hemodynamic and angiographic findings in the management of a subgroup of patients with rheumatic MS identified by clinical and noninvasive criteria, who lack clinical evidence of aortic valvular or coronary disease. Our results suggest that preoperative invasive testing is not needed in patients with moderate to severe symptoms, because cardiac catheterization rarely alters the outcome. However, patients with mild symptoms of exertional dyspnea who are considered for operation should undergo cardiac catheterization to identify hemodynamically insignificant mitral disease and thus defer or avoid surgical treatment.

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Noninvasive Diagnosis of Aortic and Mitral Valve Disease With Pulsed-Doppler Spectral Analysis

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To differentiate normal from abnormal left-sided heart valves, 34 adults (6 normal and 28 abnormal) with 48 valve lesions proved at catheterization were examined using a 3 MHz duplex pulsed Doppler echocardiograph with 2-dimensional verification of sample volume position and on-line display of the Doppler audio spectrum. A uniform protocol was used to position the sample volume for each lesion and to analyze the Doppler spectral data. Intracardiac blood turbulence, manifested by an increased Doppler spectral envelope area, was the noninvasive indicator of disease. The specific lesion present was determined by documenting the intracardiac location and timing of the turbulence. Doppler spectral envelope areas in all normal valve sites were smaller than those measured at the same sites in patients with aortic stenosis, mitral stenosis, and mitral regurgitation ($p < 0.01$). Except for a single patient with minimal aortic regurgitation, spectral envelope area allowed complete separation of patients with valve disease from normal subjects ($p < 0.01$). High sensitivity (97%) and specificity (100%) were noted despite the presence of multiple valve lesions in 67% of the patients. The data demonstrate application of a simple, noninvasive method of acquiring and analyzing Doppler echocardiographic data which allows accurate identification or exclusion of left-sided valve disease in adults, even in the presence of multiple valve lesions.

Cardiac murmurs are common in the adult population. Among patients >40 years of age, identification of significant valvular heart disease is difficult because clinical findings are influenced by associated systemic hypertension, coronary artery disease, systemic arterial disease, and other valvular heart disease.[1–13] Doppler echocardiography allows noninvasive characterization of intracardiac blood velocity patterns. According to the Doppler principle, the difference between the frequency of ultrasound broadcast into the heart and that reflected from moving blood cells (Doppler frequency shift) is proportional to the velocity of the blood cells encountered. The cylinder of ultrasound from which the Doppler signals are reflected traverses many different velocity regions in the heart. Analysis of the sum of the Doppler signals obtained along the entire ultrasound beam does not allow accurate assessment of the pattern of flow at a specific location along the beam. Range gating is required to allow operator selection of the intracardiac location to be sampled. Documentation of the anatomic region sampled (the sample volume position) is accomplished by recording the position of the sample volume on a 2-dimensional image of the heart. Knowledge of both the anatomic location of the sample volume and the characteristics of flow is required to accurately identify valvular heart disease,[14–25] especially when multiple valve lesions are present.

A simple model (Fig. 1) is helpful in understanding the blood velocity patterns near normal, stenotic, and regurgitant valves. Flow through a normal valve is characterized by blood velocities which are near the same direction and magnitude at a given time.[26,27] Because Doppler signals from areas of normal flow are near the same frequency at any time in the cardiac cycle, they are referred to as "narrow-band." As blood enters a stenotic valve, a high-velocity jet forms within and downstream from the orifice. Around and beyond the jet, turbulent flow is characterized by velocities of multiple magnitudes and directions.[26,28–29] Because Doppler signals from areas of turbulence contain many frequencies at a given time, they are referred to as "broad-band." Broad-band signals are absent downstream from normal cardiac valves, but are present beyond and alongside the high-velocity jet produced by stenotic valves.[14–20,23] Similar high-velocity jets and surrounding turbulent regions are noted near regurgitant valves.[14–17,21,22,24,25,30]

In early studies with Doppler, signal analysis was performed by human interpretation of the audio output.[14] Because experience was required to interpret such signals and a graphic record was not available to document findings, this approach did not achieve wide ac-

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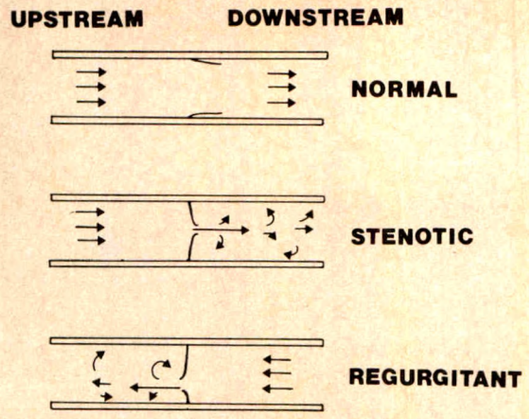

FIGURE 1. Velocity vectors, shown as arrows with magnitude and direction, illustrate blood flow patterns through normal, stenotic, and regurgitant valves. Laminar flow upstream and downstream from a normal valve is represented by parallel vectors of the same magnitude. Turbulent flow downstream from the stenotic valve and upstream from a regurgitant valve is represented by vectors with multiple directions and magnitudes.

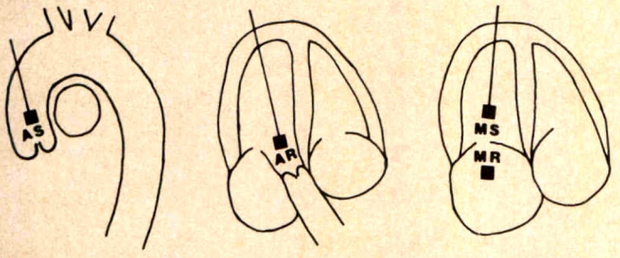

FIGURE 2. Ultrasound beam orientation and sample volume position (black square) used to diagnose aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), and mitral regurgitation (MR). Suprasternal aortic long-axis view (**left**), apical 4-chamber view at the level of the left ventricular outflows tract (**middle**), and the mitral valve orifice (**right**) are shown.

ceptance. Attempts at graphic representation of Doppler audio signal content by analog and time-interval-histogram records represented improvement,[15–18,21–25] but did not allow actual measurement of spectral broadening. Because both were susceptible to operator-induced artifacts and were less sensitive than techniques providing full spectral analysis,[31–34] they also were not widely used. Recently developed Doppler ultrasonoscopes allow not only on-line analysis of the Doppler audio spectrum, but also accurate documentation of the sample volume position on a 2-dimensional image of the heart. The purpose of this study was to demonstrate the sensitivity and specificity of such duplex Doppler ultrasonoscopes in identifying or excluding valvular heart disease in adults.

Methods

Right and left heart catheterization was the diagnostic standard of reference. The severity of aortic and mitral regurgitation was judged using the angiographic technique described by Grossman and Dexter.[35] Severity of aortic and mitral stenosis was determined by measuring resting mean systolic and diastolic pressure gradients, respectively.

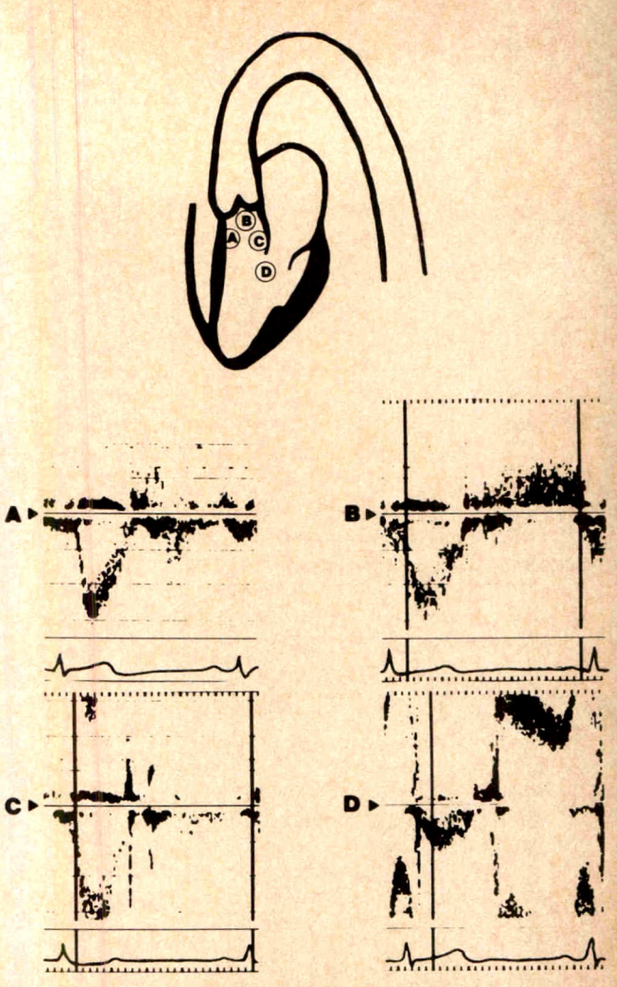

FIGURE 3. Accurate sample volume positioning is required to properly differentiate the various causes of broad spectrum diastolic Doppler signals within the left ventricular outflow tract. The **top panel** shows sample volume positions superimposed on a long-axis parasternal view of the heart. The **bottom panel** shows Doppler spectral tracings corresponding to those sample volume positions. In each spectral tracing, time is on the *x*-axis, Doppler frequency shift is on the *y*-axis, and signal amplitude is displayed as gray-scale on the *z*-axis. The electrocardiogram is shown at the bottom of each spectral tracing: **A,** wall motion artifacts produced by inclusion of the interventricular septum in the sample volume result in transient, high-amplitude artifacts in early and mid-diastole; **B,** aortic regurgitation produces pandiastolic, broad-spectrum signals when the sample volume is positioned within the regurgitant area of turbulence; **C,** mitral valve motion artifacts produced by inclusion of the anterior mitral leaflet in the sample volume result in transient, high-amplitude artifacts in early diastole; **D,** high-frequency, broad spectrum, pandiastolic signals result from placement of the sample volume in the mitral valve orifice in this patient with mitral stenosis.

Each individual was examined using a commercially available duplex 3 MHz pulsed Doppler ultrasonoscope with on-line gray-scale spectral analysis (Advanced Technology Laboratory Mark 5 with 459 Pulsed Doppler Flow Analyzer). Because there is a specific intracardiac anatomic region and cardiac cycle time during which flow disturbance would be anticipated for each valvular lesion, a standard method of examination was used (Fig. 2). To detect aortic stenosis a long-axis view of the aorta was obtained from the suprasternal notch; the sample volume was positioned in the ascending aorta about 4 cm above the aortic cusps. The apical 4-chamber

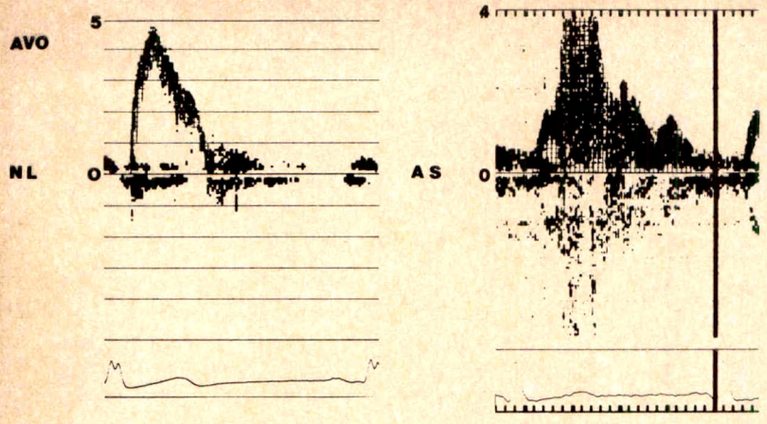

FIGURE 4. Doppler spectral records are shown from the aortic valve outflow tract (AVO) of a normal subject (NL, **left panel**) and a patient with aortic stenosis (AS, **right panel**). Time is on the *x*-axis. Doppler frequency shift (F_D) is on the *y*-axis with baseline as 0 and maximal F_D of 4 and 5 kHz; flow toward the transducer is shown above 0 and flow away is shown below 0. The electrocardiogram is in the **bottom panel.** Note systolic spectral broadening in aortic stenosis. Spectral envelope area measurement is illustrated by **cross-hatching.**

view was used to sample flow in the left ventricular outflow tract in aortic regurgitation, the mitral orifice in mitral stenosis, and the left atrium adjacent to the mitral valve in mitral regurgitation. Careful documentation of the sample volume location by 2-dimensional echocardiography was essential to determine whether broad-band diastolic Doppler signals within the left ventricular outflow tract were produced by wall or valve leaflet motion, mitral stenosis, or aortic regurgitation (Fig. 3). Wall and leaflet artifacts were <100 ms in duration and were noted when such structures were included in the sample volume; the artifact was abolished by minimal changes in beam angle and sample volume depth. The high-velocity, pandiastolic turbulence produced by mitral stenosis was of highest amplitude just downstream from the mitral orifice and never extended into the high left ventricular outflow tract. In contrast, the diastolic turbulence associated with aortic regurgitation was most marked high in the aortic valve inflow tract and diminished as the sample volume was moved toward the mitral valve orifice. Similar careful documentation of sample volume position was also essential to differentiate mitral leaflet-induced artifacts from true mitral regurgitation.

To reduce aliasing, maximal pulse repetition frequency (shallowest depth setting) possible for each examination site was selected. Wall filters were set at 100 Hz; dynamic range was set at 42. Amplifier gain was reduced to a level that would eliminate background noise but allow registration of low-amplitude signals. All spectral records were made at 100 mm/s using a gray-scale black and white strip chart recorder (Advanced Technology, model 130). Time and frequency calibration lines were generated for later reference. As the presence of turbulence was used to indicate valvular disease, the spectral envelope area, a variable that reflects both the degree and the duration of spectral broadening, was measured at each valve site. Figure 4 illustrates measurement of the spectral envelope area defined by the lowest energy systolic signals (cross-hatched area) above an aortic valve in a normal subject (left panel) and in a patient with aortic stenosis (right panel). Spectral envelope areas were measured on the channel toward which abnormal flow would be directed for each valve lesion (forward channel for aortic and mitral stenosis and aortic regurgitation; reverse channel for mitral regurgitation). Only the portion of the cardiac cycle during which abnormal flow would be produced by a given valve lesion was included in the measured spectral envelope area (systole for aortic stenosis and mitral regurgitation; diastole for mitral stenosis and aortic regurgitation). Spectral envelope areas were reported in kilohertz × seconds.

All noninvasive measurements were analyzed by individuals who did not have knowledge of catheterization results at the time of data extraction. Student's *t* test was used to demonstrate differences in mean values for the spectral envelope area between normal and diseased valves at each examination site.

Results

The study group consisted of 34 patients: 6 were normal and 28 had 48 valvular lesions proved at cardiac catheterization. Combined disease of native aortic and mitral valves was noted on catheterization in 4 patients (2 had aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation; 1 had aortic stenosis, aortic regurgitation and mitral regurgitation; 1 had

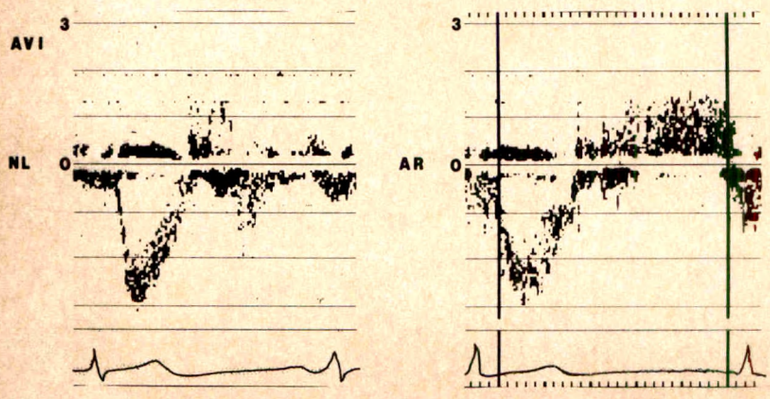

FIGURE 5. Doppler spectral records from the left ventricular outflow tract of a normal subject (NL, **left panel**) and a patient with aortic regurgitation (AR, **right panel**) are shown using the same format as in Figure 4. Note the diastolic spectral broadening in aortic regurgitation.

TABLE I Catheterization and Doppler Echocardiographic Data Summary for Native Valves Only*

Valve Site	n	ΔP	Regurg	Spectral Envelope Area (kHz × s)	p
AS					
Absent	11	0	...	0.11–0.30 (0.26)	<0.01
Present	15	10–103 (36)	...	0.72–1.72 (1.26)	
AR					
Absent	12	...	0	0.13–0.49 (0.32)	<0.01
Present	14	...	1+–3+	0.12–2.58 (1.45)	
MS					
Absent	22	0	...	0.13–0.64 (0.34)	<0.01
Present	5	8–17 (13)	...	0.75–1.68 (1.05)	
MR					
Absent	17	...	0	0.04–0.34 (0.24)	<0.01
Present	10	...	1+–4+	0.63–2.07 (1.11)	

* Mean values in parentheses.
AS = aortic stenosis; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation; n = number of patients in whom both catheterization and Doppler data are available for each valve lesion; ΔP = mean transvalvular pressure gradient in mm Hg; Regurg = regurgitation (0 = absent; 1+ to 4+ severity); kHz × s = kilohertz seconds.

aortic regurgitation and mitral regurgitation). Of 23 patients who had disease of a single valve, 14 had combined aortic regurgitation and aortic stenosis, 3 had mitral stenosis and mitral regurgitation; only 6 patients had a single lesion involving a single valve. Fifteen patients had aortic stenosis with mean systolic pressure gradients of 10 to 103 mm Hg (mean 36); 5 had mitral stenosis with mean diastolic pressure gradients of 8 to 17 mm Hg (mean 13). Angiographic evidence of aortic regurgitation was present in 14; mitral regurgitation was proved in 10. Four patients had prosthetic aortic valves: 2 had aortic regurgitation and 2 had mild aortic stenosis.

High-quality Doppler recordings were obtained in 113 of 119 (95%) examination sites in which they were attempted. They were not available from 6 additional sites (5%) because of technical difficulty in obtaining adequate 2-dimensional echocardiographic images and/or adequate Doppler signals from the suprasternal notch (3) or the cardiac apex (3).

The data in Table I are grouped to illustrate the usefulness of the spectral envelope area in separating patients with a given valve lesion from those without it. There is complete separation of spectral envelope areas with no overlap between normal subjects and patients with aortic stenosis, mitral stenosis, and mitral regurgitation of native valves; overlap in spectral envelope area between a single patient with mild aortic regurgitation and the normal population is noted. For each examination site shown, there was statistically significant separation of mean values for spectral areas between normal and diseased patients ($p < 0.01$). Sample volume localization and registration were adequate to allow correct exclusion of aortic regurgitation in both patients with mitral stenosis and no aortic regurgitation; mitral stenosis was correctly excluded in all 8 patients with aortic regurgitation and no mitral stenosis.

Figures 4 through 7 illustrate Doppler audio spectral recordings characteristic of normal (left) and diseased (right) valves for each examination site. Doppler signals from the aortic valve outflow tract are narrow-band in the absence of a pressure gradient across the aortic valve; in the presence of aortic stenosis, spectral broadening is evident throughout systole (Fig. 4). In the absence of aortic regurgitation, Doppler records from the left ventricular outflow tract show narrow-band flow away from the transducer during systole; little flow is evident during diastole. In the presence of aortic regurgitation, broad-band spectral tracings are present throughout diastole (Fig. 5). Normal Doppler signals from the mitral valve outflow tract are characterized by a narrow-band spectral record that peaks early in diastole, decreases markedly in mid-diastole, and increases in late diastole with atrial contraction. In the presence of mitral stenosis, both mean and mid-diastolic Doppler frequencies are elevated; spectral broadening is evident throughout diastole (Fig. 6). Doppler signals from the mitral valve inflow tract are near zero during systole in normal subjects; when mitral regurgitation is present, broad-spectrum pansystolic recordings are noted (Fig. 7).

Of the 4 patients with prosthetic aortic valves, 2 had aortic regurgitation and 2 had no aortic regurgitation; all 4 were correctly classified using spectral envelope area ranges derived from native valves. Two prosthetic aortic valves had significant systolic transvalvular gradients (12 and 24 mm Hg); 1 had no gradient and another had a 3-mm Hg gradient. All 4 had systolic spectral envelope areas that were above values for normal native valves.

Discussion

The blood flow disturbance produced by a diseased heart valve is similar to that resulting from stenosis of a peripheral artery.[26–30,36] Within and immediately downstream from the stenotic valve, blood velocity is elevated; beyond and alongside the area of high velocity, blood flow is turbulent. Both turbulence and high-velocity flow may serve as markers of valvular heart disease. Doppler spectral broadening and high Doppler frequency shift would be the corresponding manifestations of disease.

The timing and location of the intracardiac flow disturbance produced by valve stenosis are similar to those of laminar flow through normal aortic and mitral valves. Thus, identification of valve stenosis depends on the detection of intracardiac flow disturbance at the

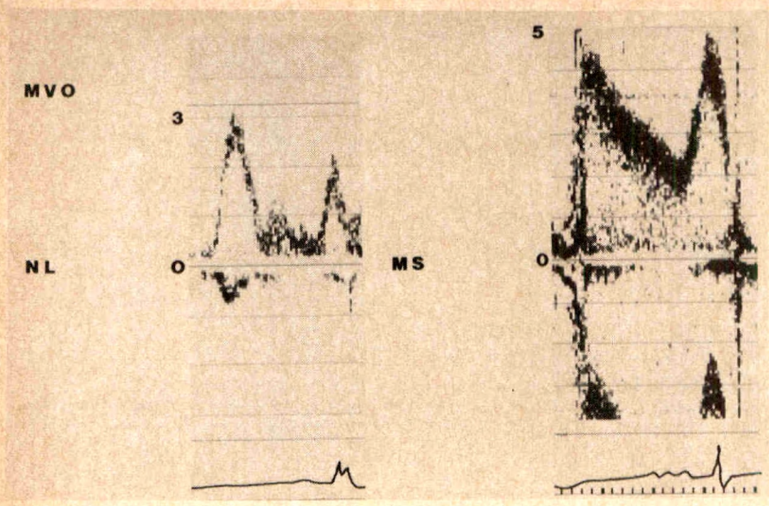

FIGURE 6. Doppler spectral records from the mitral valve outflow tract (MVO) of a normal subject (NL, **left panel**) and a patient with mitral stenosis (MS, **right panel**) are shown using the same format as in Figure 5. Note the diastolic spectral broadening and increased F_D in mitral stenosis.

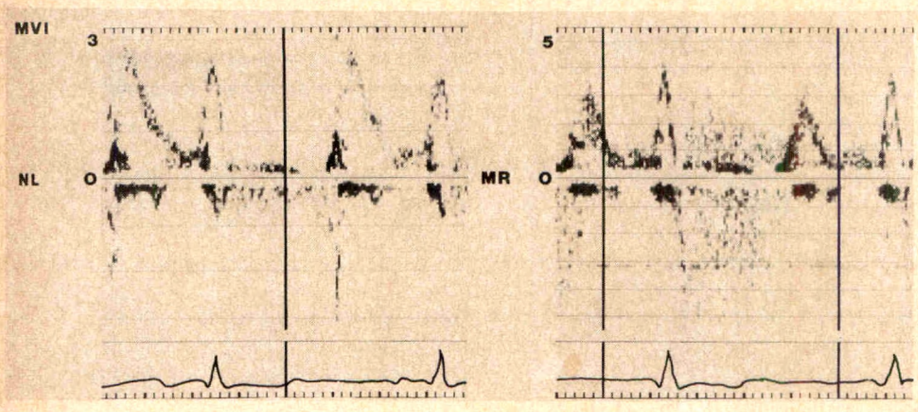

FIGURE 7. Doppler spectral records are illustrated from the mitral valve inflow tract (MVI) on the left atrial side of the mitral leaflets of a normal subject (NL, **left panel**) and a patient with mitral regurgitation (MR, **right panel**) using the same format as in Figure 5. Note the pansystolic spectral broadening in mitral regurgitation.

same time and location that normal flow would be anticipated. By contrast, valve regurgitation may be detected by finding abnormal location, direction, or timing of blood flow. Diastolic flow disturbance just below the aortic valve leaflets signifies aortic regurgitation and reflects the flow disturbance "upstream" from the regurgitant defect in the aortic valve cusp. Similarly, abnormal systolic flow induced by the defect in the mitral valve is detected on the left atrial side of the mitral leaflets.

If detection of extremely high-velocity flow is the diagnostic approach taken to detect valvular disease, continuous wave Doppler or very high pulse-repetition frequency pulsed Doppler instrumentation must be employed to avoid aliasing. Continuous wave Doppler has been useful in detecting aortic stenosis[37–39] as well as other left-sided valvular lesions.[40–42] Unfortunately, continuous-wave Doppler samples velocities along the entire ultrasound beam, not just at a selectable location. In addition, combined 2-dimensional cardiac imaging and continuous wave Doppler are not possible. Both problems may lead to ambiguity as to the exact source of the flow disturbance. Confusion would be anticipated in separating mitral stenosis from aortic regurgitation as the cause of diastolic flow disturbance in the left ventricular outflow tract. The greatest difficulty is anticipated when both lesions are present or when 1 or both are severe.

When detection of turbulence manifest by spectral broadening is used as the diagnostic indicator of disease, range-gating and registration of the intracardiac position of the sample volume are possible because Duplex pulsed-Doppler systems may be used. The importance of range-gating and accurate sample volume registration is illustrated by our ability to differentiate those patients in whom diastolic turbulence in left ventricular outflow tract was due to mitral stenosis versus aortic regurgitation. The technique involves noting changes in the severity of turbulence as the sample volume is moved from just below the aortic valve to the mitral valve outflow tract. In the presence of aortic regurgitation, the turbulence is most severe just below the aortic valve in the left ventricular outflow tract; in mitral stenosis, the turbulence is most evident near the mitral orifice. In our patient population both patients with mitral stenosis and no aortic regurgitation, all 8 patients with aortic regurgitation and no mitral stenosis, and both patients who had aortic regurgitation and mitral stenosis were correctly identified. No false-positive results were noted.

Previous studies have shown pulsed Doppler echocardiography to be reasonably accurate in detecting

mitral and aortic valve disease. Unfortunately, the equipment used in each of these previous reports required advanced operator skills to (1) interpret the Doppler audio signals used to indicate disease, (2) avoid artifacts due to improper gain settings on the representation of the spectral analysis, and (3) avoid inaccuracies in sample volume position inherent in M-mode visualization of cardiac anatomy.[14–25,31–34] Our study demonstrates the high degree of accuracy (specificity 100%; sensitivity 97%) possible when 2-dimensional echocardiographic registration of sample volume position and spectral analysis are combined; extensive training in audio recognition of abnormal Doppler signals is no longer required.

Quantification of the severity of aortic and mitral stenosis has been demonstrated with both continuous wave and pulsed-Doppler techniques. Using continuous wave Doppler, Hatle and others[38–42] found an excellent correlation between the severity of the pressure gradient across the mitral and aortic valves and the peak velocity detected. Spectral variables that reflect timing and severity of turbulence may be extracted from pulsed-Doppler signals; they correlate equally well with the severity of aortic stenosis.[43] Measurement of the volume distribution of flow disturbance, using pulsed-Doppler techniques, has been useful in determining the severity of mitral[25] and aortic[44] regurgitation. Because the emphasis of the study was on the precise definition of specific valvular pathology in adults with multiple valve disease and prosthetic valves, such complex data acquistion and signal processing techniques useful in quantifying severity were not employed.

Our data demonstrate a simple, highly accurate method of using currently available transcutaneous pulsed Doppler with spectral analysis and accurate location of sample volume position to detect or exclude the presence of aortic and mitral regurgitation and stenosis in adult patients. Detection depends on careful localization and timing of regions of turbulence within the heart. The area of the Doppler spectral envelope appears to be a useful indicator of turbulence and allows differentiation of diseased from normal valves. Correct identification of the site and type of valvular lesion remains accurate, even in the presence of multiple lesions. Preliminary data also suggest the usefulness of the technique in identifying aortic regurgitation in prosthetic aortic valves.

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Long-Term Results of Tricuspid Valve Replacement And the Problem of Prosthetic Valve Thrombosis

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Observations in 71 patients having tricuspid valve replacement over a 14-year period are described. The operative mortality rate was 10% and the actuarial survival rate was 73% at 5 years and 47% at 10 years. Survival was unaffected by the number of valves replaced or the type used (27 Starr-Edwards, 32 Björk-Shiley, 8 Lillehei-Kaster, and 4 porcine xenografts). Complications were common: 3 deaths were related to anticoagulation and 1 was due to a systemic embolus. Six patients required permanent pacing.

There was a very high incidence of thrombosis of the prosthetic tricuspid valve. Twenty percent of the tilting disc valves thrombosed, compared with 4% of the Starr-Edwards valves ($p < 0.05$). Symptoms of thrombosis were usually insidious, and its diagnosis was often delayed. There was a continuing risk of this complication, and presentation occurred up to 12 years after the original operation. Thrombolytic therapy with streptokinase was successful in 1 of 2 patients. Replacement of the thrombosed prosthetic valves was carried out without mortality in 8 patients.

Surgical correction of tricuspid regurgitation is usually considered in patients having mitral valve replacement for severe congestive cardiac failure. In most patients tricuspid regurgitation is secondary to dilatation of the tricuspid anulus and would be expected to resolve after successful mitral valve replacement.[1] In our experience, however, the tricuspid regurgitation did not resolve and in some patients became more severe. In 1966, our policy was to repair the tricuspid valve in patients shown at cardiac catheterization to have significant tricuspid regurgitation. Early experience with anuloplasty was disappointing, so most patients had tricuspid valve replacement. This report describes our experience with 71 patients who underwent tricuspid valve replacement.

Methods

Between July 1966 and January 1980, 71 patients underwent tricuspid valve replacement. The operations consisted of 1 single valve, 33 double valve, and 37 triple valve replacements. Eight operations were necessary for thrombosed tricuspid valves. Four types of valves were used in the tricuspid position: 27 Starr-Edwards, 32 Björk-Shiley, 8 Lillehei-Kaster, and 4 porcine xenografts. The hospital records of the patients were analyzed for preoperative clinical status (New York Heart Association classification), cardiac catheterization data, and data relative to the immediate and late postoperative course. Follow-up study of those patients not attending the hospital was achieved by written and telephoned questionnaire of the patient's own physician. Particular emphasis was placed on the incidence of embolization, bleeding, anticoagulant control, and valve thrombosis. In this way, it was possible to obtain the total mortality figure. Follow-up of all living patients with respect to clinical status was also achieved. In some patients who had died, data on their antemortem clinical status were incomplete. Actuarial survival curves were constructed according to the method described by Cutler and Ederer,[2] and the statistical analysis was carried out using the method of Oleinick and Mantel[3] for incidence density data. A provisional recommendation for tricuspid valve replacement was made on the basis of clinical findings, cardiac catheterization data, and right ventricular angiogram. Tricuspid regurgitation was confirmed at operation. Occasionally, tricuspid regurgitation was not considered significant until difficulty was encountered in maintaining an adequate circulation after replacement of the other valves. Until October 1977, operations were carried out under cardiopulmonary bypass with moderate hypothermia to 30°C together with aortic cross-clamping and coronary perfusion during replacement of the aortic and mitral valves. Since October 1977, cold cardioplegia and topical hypothermia have been used without coronary perfusion. Postoperative anticoagulation therapy with warfarin sodium is started on the second post-

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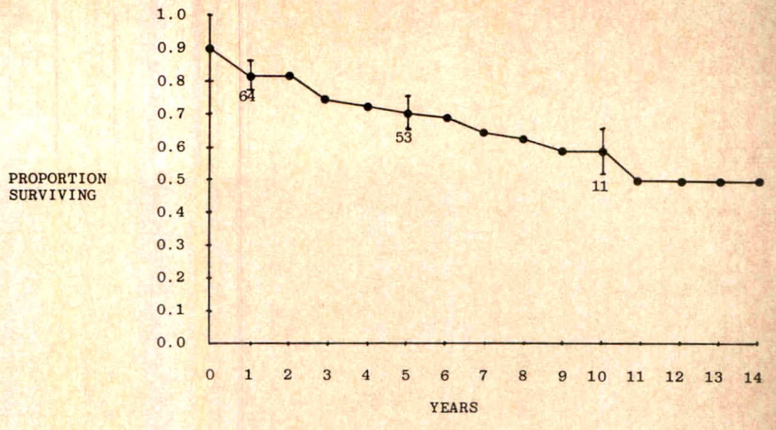

FIGURE 1. Actuarial survival curve with 95% confidence limits for all patients (n = 71) undergoing tricuspid valve replacement.

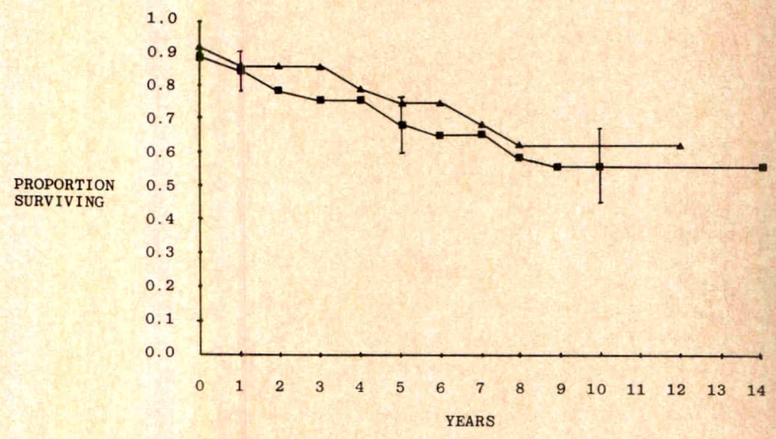

FIGURE 2. Actuarial survival curve for patients undergoing double (n = 33) and triple (n = 37) valve replacements, demonstrating no difference between the 2 groups. **Triangles** = double valve replacement; **squares** = triple valve replacement.

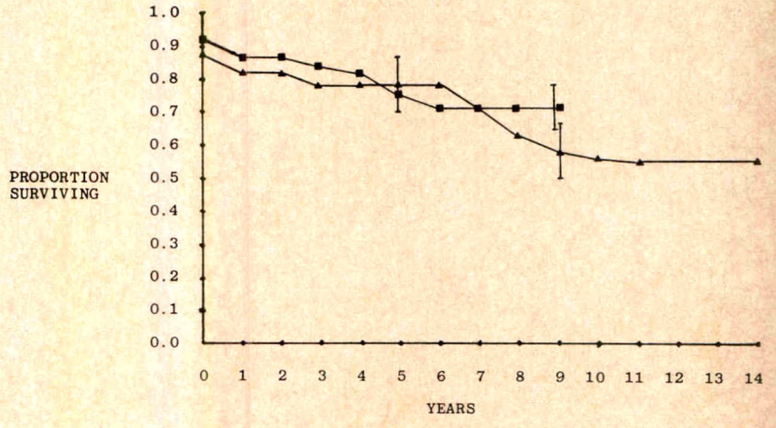

FIGURE 3. Actuarial survival curve for patients having tricuspid valve replacement with Starr-Edwards (n = 27) valves 6120 and tilting disc (n = 40) valves (Björk-Shiley and Lillehei-Kaster), demonstrating no difference between the 2 groups. **Triangles** = Starr-Edwards valves; **squares** = tilting disc valves.

operative day unless contraindicated. All patients are on permanent anticoagulant therapy. The prothrombin time is estimated monthly and is maintained at 2 to 3 times the control time.

Results

The operative mortality rate was 10%, with 7 hospital deaths, 4 of which were due to persistent cardiogenic shock. One death was due to undiagnosed asymmetric septal hypertrophy, resulting in malfunction of the Starr-Edwards mitral prosthesis because of disproportion. One death was due to pericardial tamponade and 1 death to pulmonary embolus after intractable postoperative hematemesis.

Actuarial survival curves for the 71 patients are shown in Figure 1. Survival is 86% at 1 year, 73% at 5 years, and 47% at 10 years. There was no difference between double and triple valve replacements in terms of survival (Fig. 2), nor was there any difference in survival between patients with Starr-Edwards valves and those with tilting disc valves (Fig. 3). This finding was unexpected, as the Starr-Edwards valve was used

TABLE I Cardiac Index (liters/min/m²) Pulmonary Arterial Wedge Pressure (mm Hg) and Left Ventricular End-Diastolic Pressure (mm Hg) in Different Patient Survival Groups (Mean Values ± Standard Deviation)

	n	Cardiac Index (liters/min/m²)	PAW	LVED
Operative deaths	7	2.0 ± 0.4	21 ± 7	9 ± 5
Deaths in first year	4	2.5 ± 0.9	14 ± 9	9 ± 4
First-year survivors	53	2.1 ± 0.6	19 ± 7	11 ± 5

LVED = left ventricular end-diastolic pressure; PAW = pulmonary arterial wedge pressure.

TABLE II Complications

Complications	n	Patient Year Incidence (%)
Permanent pacemaker	6	1.2
Infective endocarditis	2	0.5
Perivalvular leak, mitral prosthesis	2	0.5
Emboli		
Minor	8	2.0
Major	4	1.0
Deaths	1	0.2
Hemorrhage		
Minor	6	1.5
Major	14	3.4
Deaths	3	0.7
Total	46	11.0

TABLE III Incidence of Thrombosis of Prosthetic Tricuspid Valves

Prosthetic Valve	Insertions (n)	Thromboses		Patient Year Follow-Up	Patient Year Incidence (%)
		n	%		
Starr-Edwards	27	1	4	200	0.5
Björk-Shiley	32	5	16	170	3
Lillehei-Kaster	8	3	38	29	10
Xenograft (8 reoperations)	12	0	0	12	0
All tilting disc	40	8	20	199	4

up to 1971 and the tilting valve thereafter. There was no relation between operative mortality and preoperative cardiac catheterization data (Table I), nor between operative mortality and preoperative New York Heart Association classification. Morbidity (Table II) demonstrates the continued risk associated with multiple prosthetic valve replacement and anticoagulation. Emboli were defined as major when sequelae were permanent and minor when they were not. Hemorrhage was considered major when the patient required admission to the hospital.

Prosthetic valve thrombosis: This complication was confined to the tricuspid valve and was common with the Lillehei-Kaster and Björk-Shiley tilting disc valves (Table III). One Starr-Edwards valve thrombosed in a patient with Ebstein's anomaly who had an extremely dilated and poorly contracting right ventricle. To date, no cases of thrombosis of porcine xenografts have occurred during their shorter follow-up period. The difference between the incidence of late thrombosis with tilting disc and Starr-Edwards valves is significant ($p < 0.05$). Brief clinical details of the affected patients are given in Table IV. It can be seen that there is a continuing risk of this complication with presentation as late as 11 years after operation. In contrast to the acute presentation of thrombosis of a mitral valve prosthesis, the onset of symptoms with the tricuspid valve was usually insidious. Edema was noted in 8 patients and breathlessness in 5. The duration of symptoms ranged from 2 weeks to 1 year, with only 2 patients having symptoms for <1 month. Patient 2 had no symptoms referable to the tricuspid valve thrombosis, which was only detected during routine clinical examination. Physical examination revealed a markedly elevated jugular venous pressure in all 9 patients, reduced valve sounds in 5, and tricuspid diastolic murmurs in 8. The patient in whom a diastolic murmur was not detected was extremely obese.

Cardiac catheterization (Table IV) demonstrated a high right atrial pressure in all patients. The mean tricuspid valve gradient ranged from 5 to 18 mm Hg. Right atrial angiography invariably showed slow atrial

TABLE IV Clinical and Cardiac Catheterization: Details of Patients with Tricuspid Valve Thrombosis

Case	Age (yr)	Prosthesis	Site	Years to Reoperation	Symptoms	Duration (mo)	DM	Valve Sounds	RAP (mm Hg)	TVG (mm Hg)	CI (liters/min/m²)
1	24	S-E	T	12	Dyspnea	4	0	N	11	14	2.0
2	44	L-K	A,M,T	4	Systemic embolus	0	2/6	N	14	9	3.4
3	51	L-K	A,M,T	1	Dyspnea, CCF, Ascites	6	2/6	N	16	. . .	2.4
4	45	L-K	A,M,T	5	Ascites, Edema	0.5	4/6	N	18	13	1.3
5	55	B-S	M,T	6	Edema	12	4/6	R	18	12	. . .
6	64	L-K B-S	M T	1.5	Dypsnea, Edema	1	4/6	R	17	8	1.2
7	34	B-S	M,T	5	Dyspnea, Edema	12	3/6	R	6	5	2.0
8	63	S-E B-S	M T	8	Dyspnea, Edema	6	2/6	R	15	18	2.2
9	61	B-S	M,T	6	Edema	9	2/6	R	12	10	1.5

A = aortic; B-S = Björk-Shiley; CI = cardiac index; DM = diastolic murmur; L-K = Lillehei-Kaster; M = mitral; N = normal; R = reduced; RAP = right atrial pressure; S-E = Starr-Edwards; T = tricuspid; TVG = mean tricuspid valve gradient.

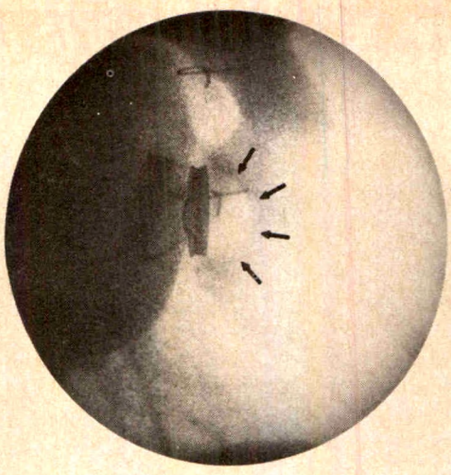

FIGURE 4, left. Right atrial angiogram in Patient 4. The large filling defect (**arrow**) is due to a thrombus on the tricuspid valve.

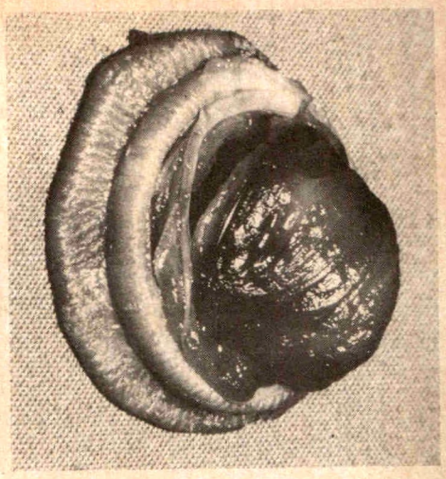

FIGURE 5, right. Operative specimen corresponding to the angiographic findings in Figure 4.

emptying, but demonstrated thrombus in only 1 patient (Fig. 4). The operative findings in this patient are shown in Figure 5. Streptokinase therapy was used in 2 patients, both of whom had symptoms suggesting tricuspid valve thrombosis for more than 6 months. The patient treated successfully had return of valve sounds after 24 hours of treatment. Right-sided pressure recordings before and after treatment are shown in Figure 6. In the second patient, thrombolytic therapy failed. At operation the valve was found to be obstructed by the septal leaflet of the native tricuspid valve. No mortality was associated with reoperation carried out in 8 patients.

Discussion

The operative mortality of 10% compares favorably with other reported mortalities of 11 to 14%.[4–9] In contrast to findings in other reports,[4,7,8] no relation appeared to exist between the preoperative New York Heart Association classification and early or late mortality.

Although the continuing morbidity of patients with prosthetic valves is well known, the incidence of thrombosis of these valves in the tricuspid position is surprisingly high. The tricuspid valve seems to be particularly vulnerable to this complication, which can occur many years after the original operation.[10–15] Poor anticoagulant control was perhaps a factor in 4 patients. Lower pressures on the right side of the heart with slower blood flow across the tricuspid valve must be important factors. In patient 8 there was an anatomic reason in that the residual septal leaflet interfered with the opening of the disc (Fig. 7). The leaflet was initially mobile, but gradually fibrosed into a band, restricting disc movement.

The significantly higher incidence of tricuspid valve thrombosis with the tilting disc valves compared with the Starr-Edwards valves has not previously been reported. It could be expected from experience with these valves in the mitral position. The situation with tricuspid valve thrombosis is much less dramatic, because a sudden large increase in right atrial pressure merely results in peripheral edema. All but 1 patient had an insidious presentation, usually with gradually increasing edema and dyspnea on exertion.

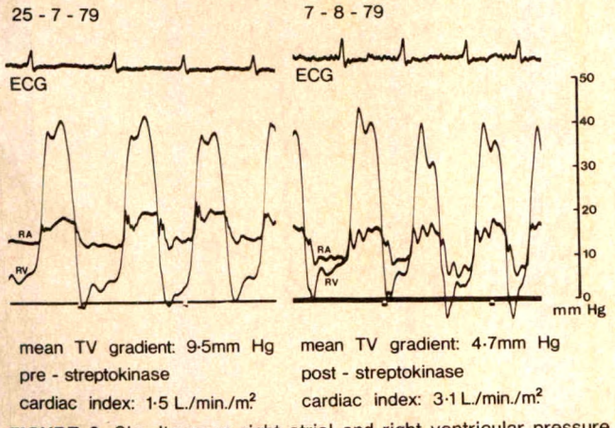

FIGURE 6. Simultaneous right atrial and right ventricular pressure tracings in patient 9, demonstrating marked reduction in tricuspid valve gradient and increase in cardiac output after streptokinase therapy. ECG = electrocardiogram; TV = tricuspid valve.

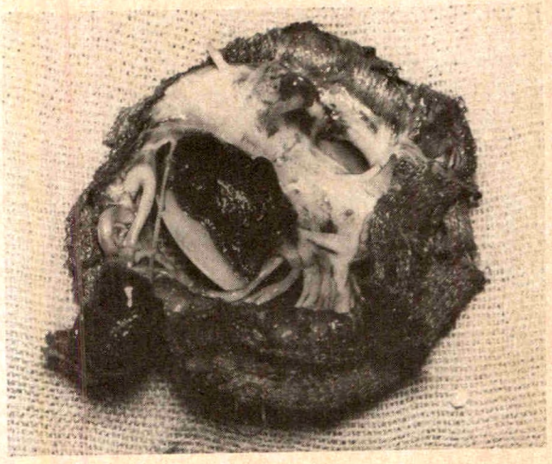

FIGURE 7. Operative specimen from patient 8. The septal leaflet of the native tricuspid valve interferes with the opening of the prosthetic valve.

Physical examination demonstrated significantly increased jugular venous pressure in all cases. All but 1 patient had a diastolic murmur that was high pitched in patients with a large gradient. The intensity of valve sounds was reduced in 5 patients.

Tricuspid valve thrombosis must be distinguished from thrombosis of a left-sided valve which is usually a much more dramatic event with marked left-sided failure. Because of their insidious presentation, with dyspnea and edema, many of the patients were thought to have myocardial failure. The distinction was made by the lack of pulmonary congestion on chest X-ray and by the demonstration of good left ventricular function on echocardiography. In our experience, the echocardiogram has otherwise proved to be disappointing in the diagnosis of thrombosed valves. The diagnosis of thrombosis was confirmed at cardiac catheterization by the demonstration of a significant gradient across the tricuspid valve in 8 patients (Table IV). In only 1 patient was a thrombus visualized at angiography (Fig. 5 and 6).

With the possibility of using streptokinase therapy,[16,17] the diagnosis must be made as early as possible so that treatment can be initiated before organization and fibrosis of the thrombus has occurred. The patients reported on in the literature have all had recent thrombosis, although our successfully treated patient had a history suggestive of thrombosis for 9 months before treatment.

Although Braunwald et al[1] reported that functional tricuspid regurgitation usually resolved after successful surgery, subsequent experience does not support this finding. Increasing use was made initially of tricuspid valve replacement and subsequently of tricuspid valve anuloplasty and valvuloplasty. Although initially there was some disagreement as to which of these techniques gives the best results, there is now wide acceptance of the conservative management of tricuspid regurgitation.[18,19] At our institution, it is now rare to replace the tricuspid valve, and the most common indication since 1976 has been thrombosis of a prosthetic valve.

Porcine xenograft is now the valve of choice in tricuspid valve replacement. However, thrombosis has been reported in the immediate postoperative period in patients with very low cardiac output,[20] and Horowitz[21] demonstrated that the porcine valve opens poorly under low pressure. In our limited follow-up, there have been no instances of thrombosis. The Björk-Shiley and Lillehei-Kaster valves must be considered unsuited to the tricuspid position because of their tendency to thrombotic obstruction. The Starr-Edwards valve had only a low incidence of thrombosis, although there have been several reports in the literature.[7,8,10–13] In most of these reported cases, there was an anatomic cause for the thrombosis, usually a strut of the valve being embedded in the muscle of the right ventricle. In the mitral position, thrombosis of the Starr-Edwards valve is rare. Thromboembolism is the more common problem, and on the right side of the heart infrequent small emboli are not likely to be a problem in the pulmonary circulation. Our data indicate that Starr-Edwards valve 6120 is a satisfactory valve for the tricuspid position, especially when the patient is young and requires anticoagulant therapy.

Conclusion: From this study the Björk-Shiley and Lillehei-Kaster tilting disc valves prove to have an unacceptably high rate of thrombosis in the tricuspid position. Starr-Edwards valve 6120 and the porcine xenograft appear to be satisfactory. The clinical picture of prosthetic tricuspid valve thrombosis has been described as an insidious one, with the diagnosis often being delayed. Treatment with streptokinase may be successful. Reoperation can be undertaken with a low risk.

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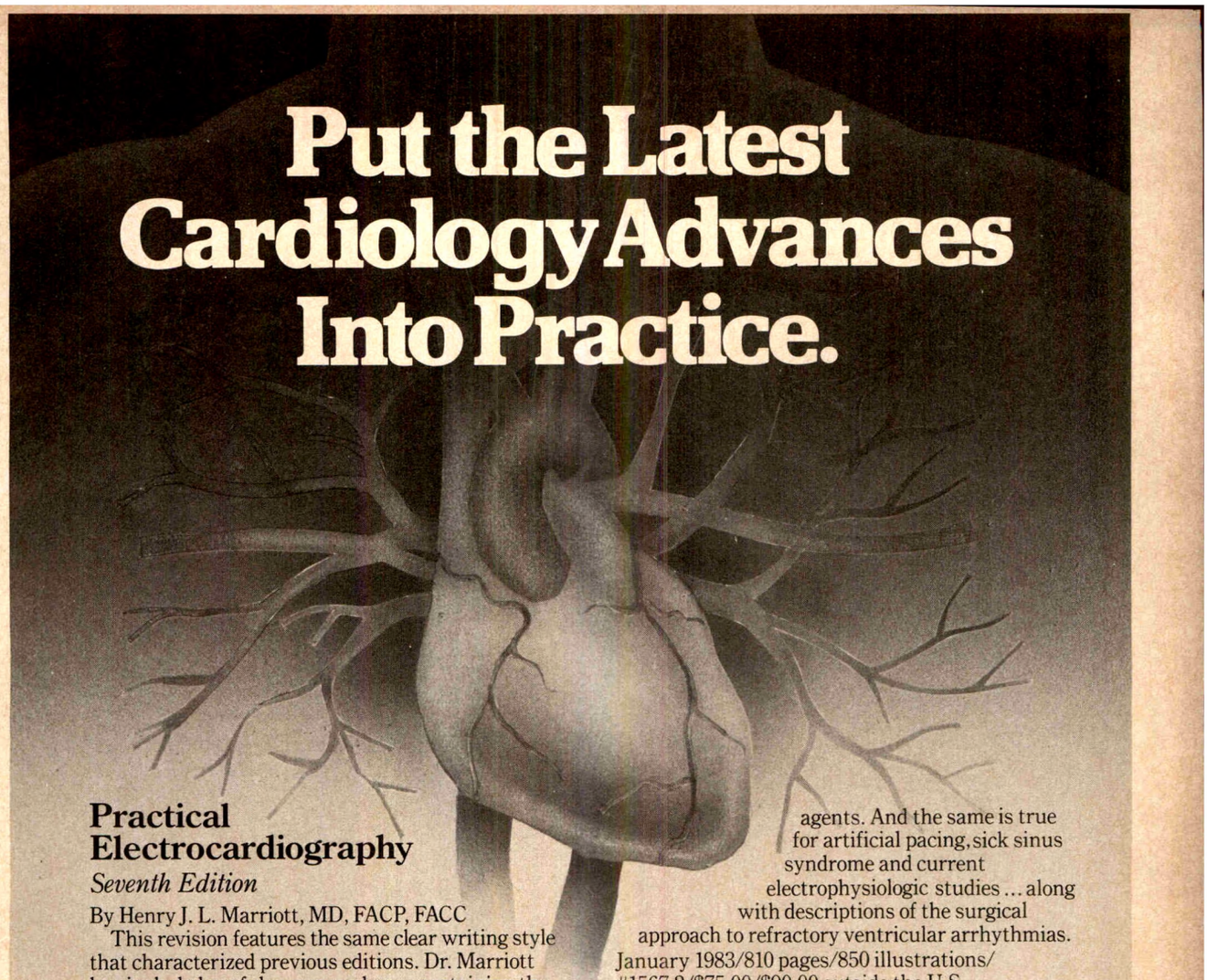

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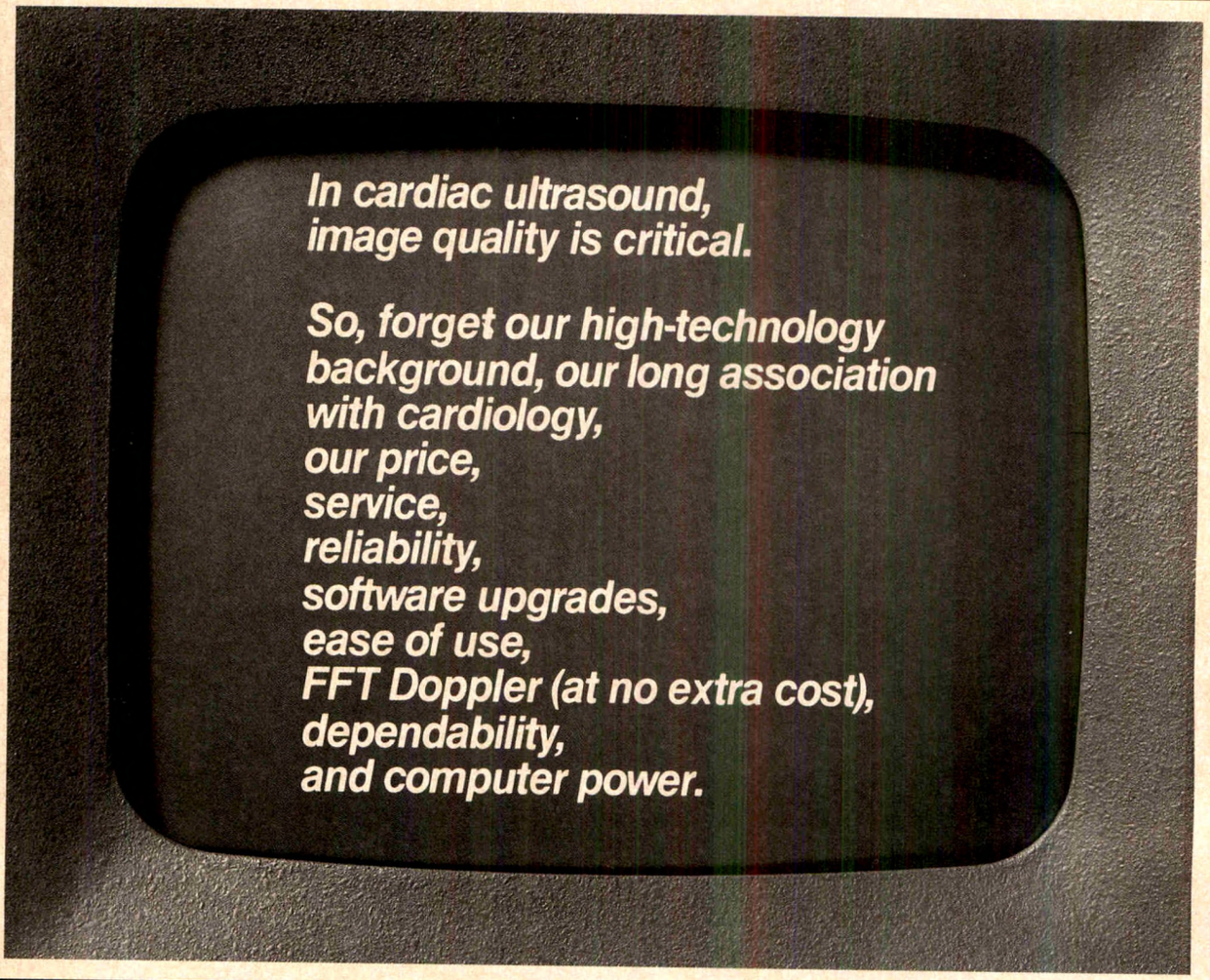

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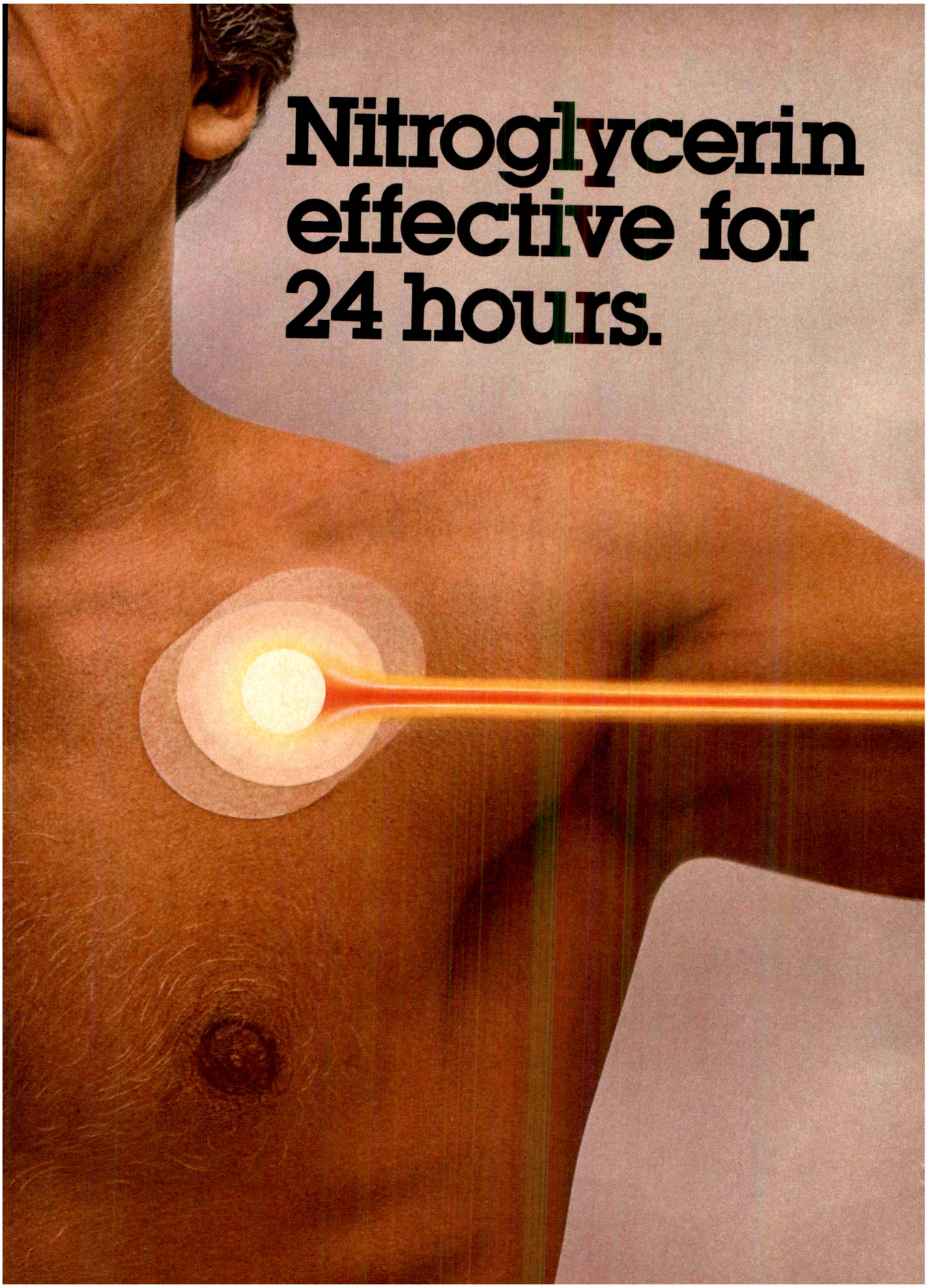
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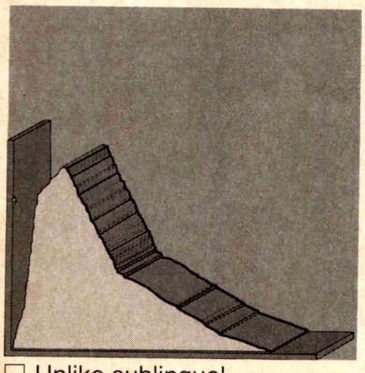

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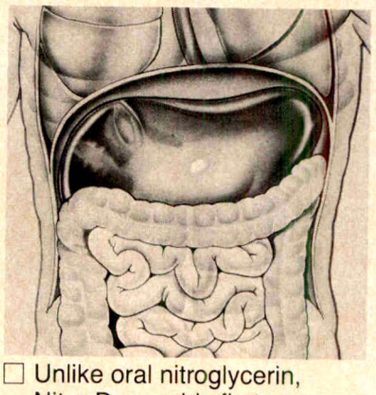

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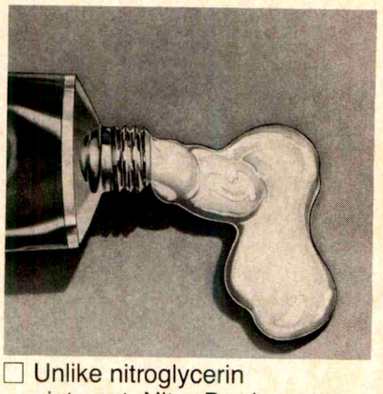

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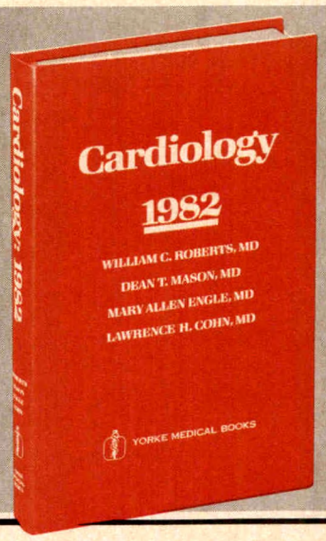

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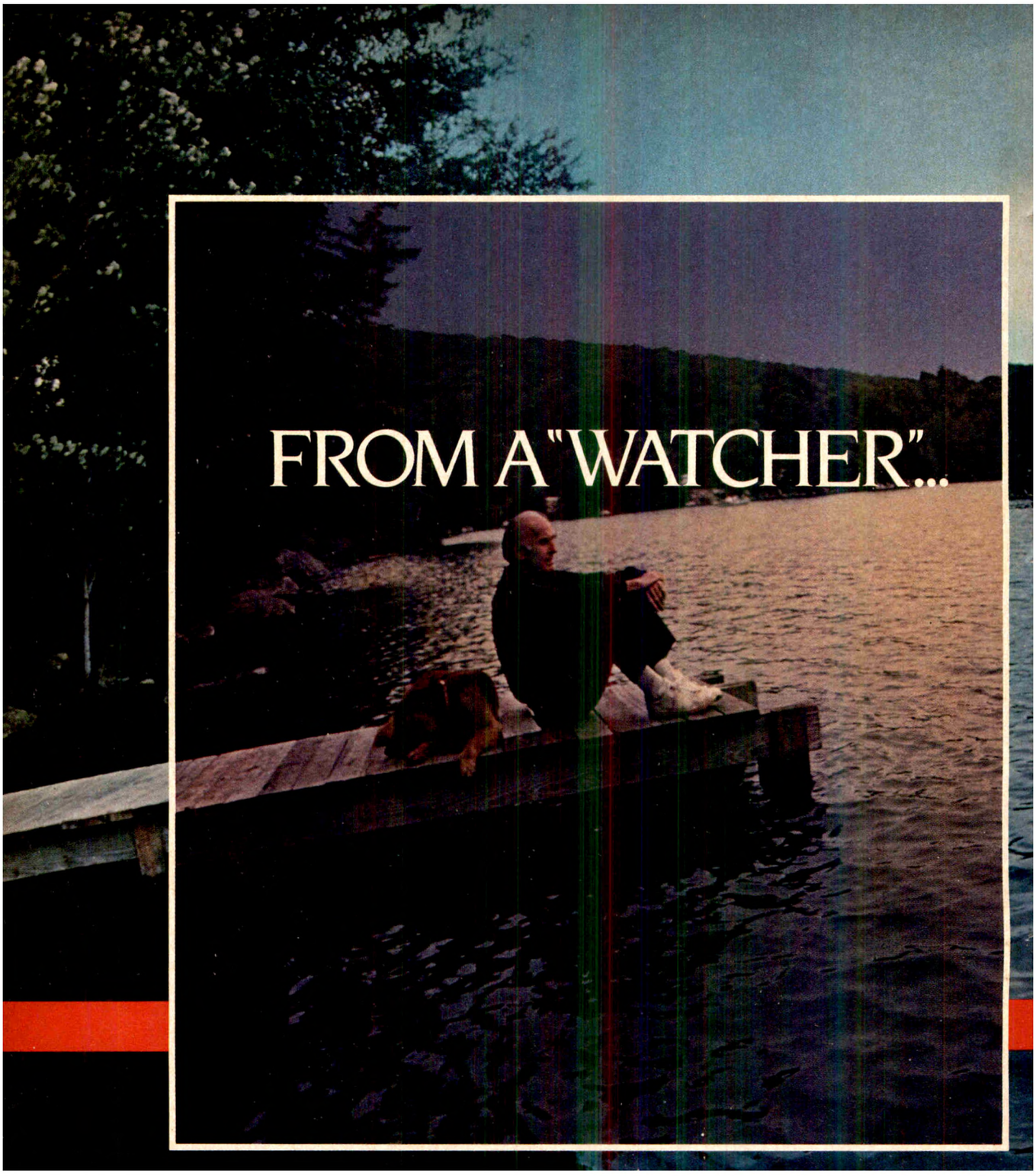
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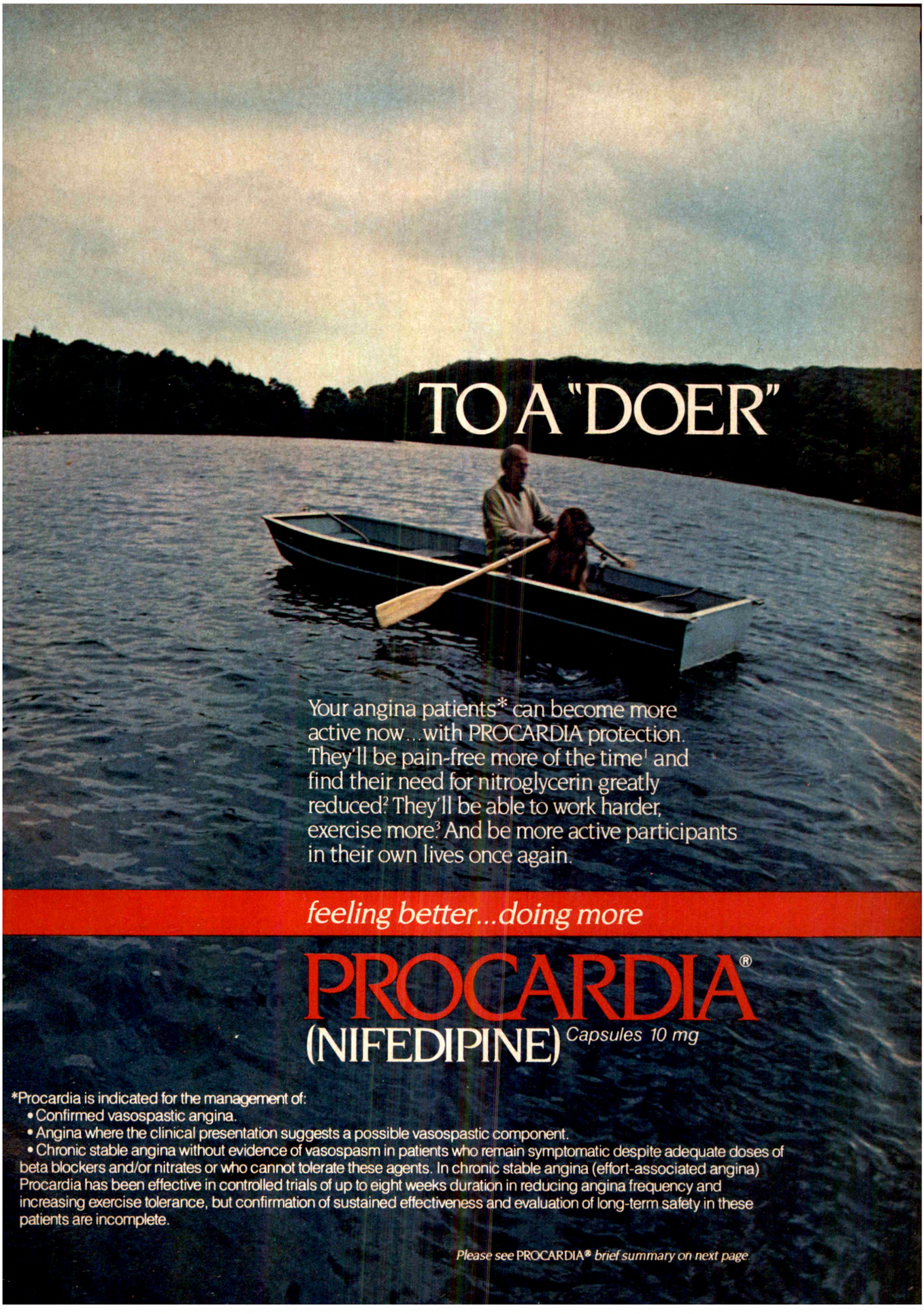

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(nifedipine)

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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Symptomatic Sick Sinus Syndrome in Children and Adolescents as the Only Manifestation of Cardiac Abnormality or Associated With Unoperated Congenital Heart Disease

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Sick sinus syndrome (SSS) occurs infrequently in children who have not undergone cardiac surgery. The symptoms, electrocardiograms, and electrophysiologic data in 11 patients aged 2 to 17 years who had nonsurgical SSS were reviewed. Syncope occurred in 5 patients and sinus bradycardia in 9. Sinus nodal recovery times were prolonged in 6 patients. The atrial effective refractory period was prolonged in 2 patients and the atrioventricular nodal functional or the effective refractory period, or both, was prolonged in 5 patients. Because patients with nonsurgical SSS may have abnormalities not only of the sinus node but also of the atrium and the atrioventricular node, it is recommended that patients with symptomatic SSS be evaluated by electrophysiologic study. The proper choice of antiarrhythmic drug therapy or permanent pacing procedure depends on a complete analysis of the cardiac conduction system.

Sick sinus syndrome (SSS) after corrective surgery for congenital heart disease has been reported by numerous investigators.[1–5] SSS has been reported less frequently in pediatric patients with either unoperated congenital heart disease[6,7] or with structurally normal hearts.[8–11] This investigation reviews our experience with nonsurgical SSS.

Methods

We reviewed the charts of our patients diagnosed as having SSS between 1972 and 1981. Patients who had SSS after open or closed cardiac surgery were excluded. We did, however, include 1 patient who had SSS after repair of a vascular ring. Eleven patients, aged 2 to 17 years, had nonsurgical SSS. Of these 11 patients, 8 had structurally normal hearts and 3 had either congenital or acquired heart disease.

The symptoms, resting electrocardiograms, and ambulatory electrocardiograms of each patient were reviewed. After noninvasive evaluation, each patient underwent invasive electrophysiologic study according to techniques previously described for our laboratory.[12] All cardiac medications were discontinued 24 hours before electrophysiologic study. The patients were sedated with meperidine, 2 mg/kg, and promethazine, 0.5 mg/kg, 30 minutes before study. Since this investigation spanned 9 years, our protocol has varied somewhat and not all measurements were obtained for each patient. During electrophysiologic study, we recorded the maximal corrected sinus nodal recovery time, total sinoatrial conduction time, atrial muscle effective refractory period, intraatrial conduction time (high right atrium to low septal right atrium), anterograde atrioventricular nodal functional refractory period, anterograde atrioventricular nodal effective refractory period, atrioventricular nodal conduction time (A-H), His-Purkinje conduction time (H-V), the atrial pacing cycle length at which atrioventricular nodal Wenckebach was first observed, and whether or not supraventricular tachycardia or atrial flutter or fibrillation was inducible during the study. Definitions of these refractory periods, as well as normal values, were previously reported.[12–15]

Results

Clinical features: Eight of our 11 patients had structurally normal hearts. Three had either congenital or acquired heart disease. The associated cardiac diseases were a vascular ring and small ventricular septal defect in 1 patient, an absent left pulmonary artery in another patient, and cardiomyopathy in the third pa-

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TABLE I Electrophysiologic Data

	JP	TP	BW	JM	DA	JB	SB	SE	SC	RG	DF
Max CSNRT (NI ≤275)	*	10	540	662	170	2,440	110	325	4,000	200†	2,350
SACT (NI ≤200)	*	NP	212	154	120	80	NP	NP	262	JR	215
AM ERP (NI 187 ± 53)	*	185 @ A_1-A_1 513	270 @ A_1-A_1 1,000	207 @ A_1-A_1 799	180 @ A_1-A_1 550	NP	160 @ S_1-S_1 450	210 @ S_1-S_1 850	231 @ S_1-S_1 677	JR	320 @ A_1-A_1 1,440
HRA-LSRA (NI 10–40)	30	30	20	30	50	−25‡	10	20	−20‡	JR	30
Ante AVN FRP (NI 347 ± 71)	*	NP	470 @ A_1-A_1 1,000	409 @ A_1-A_1 799	340 @ S_1-S_1 600	§	370 @ S_1-S_1 450	500 @ S_1-S_1 850	433 @ S_1-S_1 669	JR	520 @ A_1-A_1 1,420
Ante AVN ERP (NI 241 ± 56)	*	NP	400 @ A_1-A_1 1,000	292 @ A_1-A_1 793	<180 @ A_1-A_1 550	§	240 @ S_1-S_1 450	230 @ S_1-S_1 850	337 @ S_1-S_1 669	JR	≤320 @ A_1-A_1 1,440
A-H (NI 50–120)	70	80	80	70	150	95	140	90	90	JR	80
H-V (NI 25–55)	55	20	40	50	40	25	40	35	42	JR	40
Wenckebach cycle length	*	270	450	493	250	‡	300	420	370	JR	571
SVT or atrial flutter/fibrillation induced	SVT	SVT	No	No	No	SVT & atrial fibrillation	SVT	SVT	No	No	No

* Incessant supraventricular tachycardia.
† Maximal junctional recovery time.
‡ Low right atrial rhythm.
§ Presence of both Kent and James fibers in this patient prevented these measurements.

A_1-A_1 = sinus cycle length; A-H = low septal right atrium to His (atrioventricular nodal) conduction time; AM ERP = atrial muscle effective refractory period; Ante AVN ERP = anterograde atrioventricular nodal effective refractory period; Ante AVN FRP = anterograde atrioventricular nodal functional refractory period; HRA-LSRA = high right atrium to low septal right atrium (intraatrial) conduction time; H-V = His to ventricle (His-Purkinje) conduction time; JR = junctional rhythm interfered with these measurements; Max CSNRT = maximal corrected sinus nodal recovery time; NI = normal; NP = not part of our protocol at time of patient's study; S_1-S_1 = paced atrial cycle length; SACT = total sinoatrial nodal conduction time; SVT = supraventricular tachycardia.

tient. The latter patient with cardiomyopathy is the only 1 of our 11 patients who had a significant intrinsic myocardial abnormality.

The age at presentation ranged from 2 to 17 years. Nine of the 11 patients were male. Symptoms included syncope or near-syncope (5 patients), chest pain (3), palpitations (5), dizziness (3), and pallor, tachypnea, and disorientation (1).

Electrocardiographic findings: The most frequent resting and ambulatory electrocardiographic finding was sinus bradycardia (9 patients). Three patients had sinus rates <40 beats/min, and 2 of these had a sinus rate of 30 beats/min. The next most common electrocardiographic finding was supraventricular tachycardia (5 patients). Sinus pauses of up to 3.2 seconds' duration were noted in 2 patients. Wolff-Parkinson-White Syndrome (1 patient), atrial flutter (1), junctional rhythm (1), premature junctional and atrial contractions (1), and atrioventricular dissociation (2) were also seen.

Electrophysiologic evaluation of sinus nodal function: During electrophysiologic study, we assessed sinus nodal function by measurement of the maximal corrected sinus nodal recovery time and total sinoatrial conduction time (Table I). The maximal corrected sinus nodal recovery time was measured in 9 of the 11 patients. The sinoatrial conduction time was measured in 6. Sinoatrial conduction time was not determined in some patients, either because they had incessant tachycardia (JP) or junctional rhythm (RG), or because the determination of sinoatrial conduction time was not yet part of our routine protocol (TP, SB, SE). The range of maximal corrected sinus nodal recovery times was 10 to 4,000 ms. Our upper limit of normal for corrected sinus nodal recovery time is 275 ms,[16] and 6 of 9 patients exceeded this value. Three of these patients had extremely long maximal corrected sinus nodal recovery times of 2,350, 2,440, and 4,000 ms. Our upper limit of normal for sinoatrial conduction time is 200 ms[16]; only 3 of 6 patients had prolonged sinoatrial conduction times.

Electrophysiologic evaluation of atrial muscle function: We assessed atrial muscle function during electrophysiologic study by measurement of the intraatrial conduction time and the atrial muscle effective refractory period (Table I). Intraatrial conduction time (high right atrium to low septal right atrium) was only slightly prolonged in 1 of 10 patients (50 ms, DA). The atrial muscle effective refractory period was only prolonged in 2 of 8 patients.

Electrophysiologic evaluation of atrioventricular nodal function: The resting atrioventricular nodal conduction time (A-H) was only slightly prolonged in 2 of 10 patients (140 ms, SB; and 150 ms, DA). The anterograde functional refractory period of the atrioventricular node was prolonged in 4 of 7 patients. The anterograde effective refractory period of the atrioventricular node was prolonged in 2 of 6 patients. Wenckebach developed in the atrioventricular node at atrial pacing cycle lengths of ≤300 ms in 3 of 8 patients and at atrial pacing lengths of ≥420 ms in 5 of 8 patients. In our laboratory, we consider Wenckebach cycle lengths ≤300 ms (≥200 beats/min) normal and ≥400 ms (≤150 beats/min) abnormal (unpublished data).

Induction of tachycardia: We were able to induce supraventricular tachycardia in 5 of 11 patients. During electrophysiologic study, the tachycardia was induced by programmed premature atrial or ventricular stimulation, or a combination of these. The mechanism of supraventricular tachycardia was atrioventricular nodal reentry in 2 of 5 patients and atrial muscle reentry in 1 of 5 patients. In 2 of 5 patients, both a James fiber and a concealed Kent bundle (1 left Kent, 1 right anterior Kent) were present. The Kent bundle participated in the tachycardia circuit in both of these patients as demonstrated by eccentric atrial activation sequence during supraventricular tachycardia and by elimination of tachycardia after surgical division of the Kent bundle. In 1 of these 5 patients, we were also able to reproducibly induce atrial fibrillation (JB).

Follow-up and treatment: Of our 11 patients, 4 were seen at a one-time consultation only. The follow-up period ranged from 1.5 to 11 years in the remaining 7 patients (mean 4 years). Eight of our 11 patients required implantation of a permanent pacemaker. An atrial demand pacemaker was implanted in 5 of 8 patients and a ventricular demand pacemaker was implanted in 3. Of the patients who received pacemakers, 6 of 8 required no medication after pacemaker implantation. All 3 patients who did not receive pacemakers have been receiving digoxin therapy.

Discussion

Numerous criteria have been used to define SSS. Some workers diagnose SSS only when there are both electrocardiographic findings and symptoms suggesting sinoatrial nodal dysfunction.[17] Others have suggested that the presence of surface electrocardiographic or invasive electrophysiologic findings consistent with abnormal sinus nodal function, whether or not symptoms are present, is sufficient for the diagnosis of SSS.[18,16] In our patients with nonsurgical SSS, we found that the most sensitive and consistent indicator of sinus nodal dysfunction was the presence of sinus bradycardia on either the resting or ambulatory electrocardiogram. Nearly all of our patients also had syncope, palpitations, or both. During electrophysiologic study, 1 patient had a definitely abnormal sinoatrial conduction time, and the maximal corrected sinus nodal recovery time was prolonged in 6 of our patients.

Bharati et al[19] reported pathologic findings in 2 adolescents without congenital heart disease who had a history of sinus nodal dysfunction. At necropsy, each patient had an essentially normal sinoatrial node and sinoatrial nodal artery. However, each patient had significant pathologic changes in the atrial muscle and in the atrioventricular perinodal tissue. Others[20,21] have found abnormalities of the sinus node and atrial muscle in patients known to have clinical sinus nodal dysfunction. In the present series of patients with nonsurgical SSS, we have demonstrated not only common, significant abnormalities of the sinus node, but also significant albeit uncommon electrophysiologic abnormalities of the atrium. We also found mildly ab-

normal atrioventricular nodal function in many of our patients. The atrial pacing cycle length at which atrioventricular nodal Wenckebach occurred was a particularly sensitive indicator of atrioventricular nodal abnormality.

Based on our review of patients with SSS, we suggest that the presence of sinus bradycardia on resting or ambulatory electrocardiograms is the most sensitive indicator of sinus nodal abnormality. Symptoms such as syncope, palpitations, and chest pain are also nearly always present.

During electrophysiologic study, the maximal corrected sinus nodal recovery time may often be abnormally prolonged. However, some patients with sinus bradycardia and symptoms have normal maximal corrected sinus nodal recovery time. It is possible that the sedation used for our electrophysiologic studies decreases vagal tone and masks significant sinus nodal abnormalities. Our work in chronically instrumented animals found a 50% decrease in corrected sinus nodal recovery time after similar sedation.[22] In the patients in whom it was measured, the sinoatrial conduction time was a relatively insensitive indicator of sinus nodal function.

In this group of pediatric patients with nonsurgical sinoatrial nodal disease, we found a greater incidence of atrial and atrioventricular nodal disease than in our series of patients with SSS after the Mustard operation.[4] These findings, together with those of Bharati et al,[19] suggest that the process causing SSS in children not operated on is more diffuse than in patients who undergo Mustard operation. However, Vetter et al[23] found that some patients after the Mustard operation did have atrial and atrioventricular nodal disease associated with sinus nodal dysfunction. In the present series, electrophysiologic studies also confirmed tachyarrhythmias in patients with nonsurgical SSS and clarified the mechanism of these arrhythmias. Several tachyarrhythmias were found to be due to accessory connections.

In summary, we recommend that patients with either symptoms or electrocardiographic findings suggesting sinoatrial nodal dysfunction should be evaluated by electrophysiologic study. During electrophysiologic study, sinoatrial node, atrial muscle, and atrioventricular nodal function should be evaluated. Proper choice of antiarrhythmic drug therapy or permanent pacing procedure depends on a complete analysis of all components of the cardiac conduction system in patients with SSS. Although our results with both atrial and ventricular pacing have been satisfactory, the perfection of the universal pacemaker may dictate its use in these patients in the future.

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Sustained Ventricular Tachycardia After Repair of Tetralogy of Fallot: New Electrophysiologic Findings

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Ventricular arrhythmia originating from the outflow tract of the right ventricle is a presumed cause of late sudden death in patients after repair of tetralogy of Fallot. Exercise testing has been shown to enhance detection, and phenytoin has been shown to control ventricular arrhythmias in these patients. This study reports new findings in 3 patients who underwent electrophysiologic studies at postoperative cardiac catheterization; in each, sustained ventricular tachycardia was induced and found to originate from the inflow-septal area of the right ventricle. Using serial studies, the same sustained ventricular tachycardia was induced during therapeutic serum concentrations of phenytoin but not after propranolol. No patient had ventricular arrhythmia during a 24-hour electrocardiogram or during exercise. Although no patient had normal hemodynamic function, only 1 patient had right ventricular pressure greater than two-thirds systemic pressure. Each patient had undergone initial intracardiac repair at a relatively late age (3, 9, and 9 years).

An increasing amount of evidence suggests that ventricular arrhythmia originating from the right ventricular outflow area is a cause of late sudden death in patients after repair of tetralogy of Fallot.[1–5] Recent attention, therefore, has been focused on the detection, prevention, and treatment of ventricular arrhythmias in these patients.[6–16]

Detection of ventricular arrhythmias has been enhanced by utilizing exercise testing and 24-hour ambulatory tape monitoring.[5–8,10,11,13] However, few intracardiac electrophysiologic data have been correlated with the noninvasive tests, making it difficult to assess the sensitivity of these tests in detecting life-threatening ventricular arrhythmias.[14] Although phenytoin has been shown empirically effective in controlling ventricular premature beats and ventricular tachycardia (VT) in these patients,[8,13] there have been no reported intracardiac electrophysiologic studies documenting the effectiveness of phenytoin. Several studies of adult patients with VT have been reported showing a strong positive correlation between the effectiveness of an antiarrhythmic agent during electrophysiologic study and the effectiveness during clinical application.[17–20] We describe herein new electrophysiologic findings in postoperative patients with tetralogy of Fallot in whom VT was induced during electrophysiologic study.

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Methods

Patients: Sustained VT was induced during electrophysiologic studies in 3 adolescent patients: Patient 1, a 14-year-old boy, and Patients 2 and 3, 16-year-old and 14-year-old girls, respectively. Patients 1, 2, and 3 underwent initial intracardiac repair of tetralogy of Fallot at ages 9, 3, and 9 years of age, respectively. Patients 1 and 3 each underwent reoperation at age 12 years, and Patient 2 had a repeat operation at age 11 years. In Patients 2 and 3, a valved (Hancock) conduit was placed from the right ventricle to the pulmonary artery at the first operation and replaced at the second operation because of progressive stenosis between the right ventricle and the pulmonary artery. Patient 1 had a right ventricular outflow patch placed at the first operation but because of increasing cardiomegaly due to progressive pulmonary insufficiency and tricuspid insufficiency, porcine Carpentier-Edwards prosthetic tricuspid and pulmonary valves were placed at the second operation. Only Patient 2 had a residual ventricular septal defect after the first operation and, although reclosure was attempted during the second operation, a tiny residual ventricular septal defect persists.

Intracardiac electrophysiologic study: Meperidine (2 mg/kg, maximum 80 mg) and promethazine (1 mg/kg, maximum 40 mg) were administered to each patient 30 to 45 minutes before cardiac catheterization. All cardioactive drugs were

TABLE I Drug Administration and Timing of Study

Patient	Drug	Dose	Serum Concentration	Timing of Study
1	Lidocaine	2 mg/kg IV	. . .	Initial study
	Phenytoin	300 mg BID po	22 μg/ml*	3 Weeks later
	Quinidine sulfate	600 mg q 6 h po	4.2 μg/ml	2 Weeks later
	Procainamide	1,000 mg/1 h IV	7.0 μg/ml	1 Day later
	Propranolol	80 mg q 6 h po, then 0.11 mg/kg IV	154 ng/ml†	1 Day later
2	Propranolol	0.15 mg/kg IV	49 ng/ml	Initial study
	Phenytoin	15 mg/kg/day po	19 μg/ml	3 Days later
3	Propranolol	0.15 mg/kg IV	56 ng/ml	Initial study
	Phenytoin	15 mg/kg/day po	21 μg/ml	2 Days later

* Reference 21.
† Reference 22.
BID = twice a day; IV = intravenously; po = orally.

TABLE II Surface and Intracardiac Measurements*

Patient	SCL	PR	QRS	QT	HRA-LSRA	A-H	H-V	V-RVA	ERP-RV
					Baseline				
1	660	200	160	350	60	110	50	40	220 @ 500†
2	560	140	160	400	45	85	55	45	200 @ 500†
3	770	240	110	390	30	170	40	10	220 @ 500†
					After Phenytoin				
1	630	190	170	400	60	90	50	45	240 @ 500†
2	580	160	160	410	35	80	50	30	200 @ 500†
3	680	250	110	410	50	150	45	10	240 @ 500†
					After Propranolol				
1	1200	210	170	420	25	150	50	30	270 @ 600†
2	750	160	160	410	25	100	55	45	180 @ 500†
3	760	260	100	380	35	170	45	10	250 @ 500†

* All measurements in milliseconds.
† Pacing cycle length.
A-H = atrial-His; ERP-RV = effective refractory period of right ventricular muscle; H-V = His-right ventricle (inflow-septal); HRA-LSRA = high right atrium to low septal right atrium; SCL = sinus cycle length; V-RVA = right ventricle (inflow-septal) to right ventricular apex.

TABLE III Ventricular Tachycardia

Patient	CL (ms)	Induced by (ms)	Terminated by
1	220	S_2-S_3 220 (S_1-S_1 500; S_1-S_2 250)	DC CV
2	210	S_2-S_3 200 (S_1-S_1 500; S_1-S_2 250)	S_1-S_1 300
3	220	Burst (230)	DC CV

CL = cycle length; DC CV = direct-current cardioversion; S_1-S_1 = ventricular pacing cycle length; S_1-S_2 = interval ending with first premature ventricular stimulus; S_2-S_3 = interval ending with second premature ventricular stimulus.

stopped at least 36 hours before performing baseline electrophysiologic studies. The hemodynamic study was performed before and the angiographic study after the electrophysiologic studies.

Five quadripolar catheters were used in each patient during the initial electrophysiologic studies. After introduction by the percutaneous technique and under the guidance of fluoroscopy, 4 catheters were advanced through sheaths from both femoral veins and positioned in the following areas: (1) high right atrium near the sinoatrial node; (2) across the tricuspid valve orifice in order to record the low septal right atrial, His and right ventricular inflow-septal depolarizations; (3) the right ventricular apex; and (4) the right ventricular outflow tract. The interelectrode distances were 10 mm on the His catheter and 3 mm on the right ventricular apex and outflow tract catheters. For recording, the proximal pair of electrodes on the right ventricular apex catheter and the distal pair on the right ventricular outflow tract catheter (positioned anteriorly) were used and both distal and proximal pairs were used on the His catheter. Through a side-arm sheath placed in a femoral artery, the fifth catheter was advanced retrogradely and positioned in the lateral left ventricle. Surface electrocardiographic leads I, aVF, and V_1 were recorded simultaneously with the electrograms on an Electronics for Medicine photographic recorder (VR12 or VR16) at a paper speed of 100 or 250 mm/s.

Ventricular stimulation techniques: A programmable stimulator (Bloom Associates, Philadelphia) was used to deliver stimuli 1 ms in duration with amplitude approximately twice diastolic threshold (no amplitudes were >2 mA). After evaluation of the sinoatrial node, atrial muscle, atrioventricular node, and the His-Purkinje system, ventricular stimulation was performed.

Ventricular stimulation protocol: 1. Single (S_2) and double (S_2-S_3) premature stimuli were induced into a ventricular paced rhythm (2 cycle lengths: 500 and 400 ms); S_2 was coupled to the last ventricular paced beat (S_1) and S_1-S_2 was decreased by 10 to 20 ms until failure of S_2 capture (ventric-

ular muscle effective refractory period). The S_1-S_2 interval then was increased 50 to 70 ms and S_2-S_3 were initiated at the same interval, followed by successive 10 to 20 ms decrements. When failure of S_3 capture occurred, S_1-S_2 was decreased, followed again by a decrease in S_2-S_3 until both S_2 and S_3 failed to capture.

2. Rapid ventricular pacing was carried out at several cycle lengths (400 to 200 ms). At cycle lengths of 300 to 400 ms, the duration of pacing was approximately 15 to 30 seconds. To avoid hypotension associated with longer duration of pacing at the shorter cycle lengths, bursts of 8 paced beats were given. No fewer than 5 bursts were given at each cycle length (range of cycle length 280 to 200 ms).

Administration of antiarrhythmic drugs and timing of electrophysiologic studies: After baseline study, serial drug-electrophysiologic studies were carried out in the sequence listed in Table I. A drug was considered successful when no more than 2 reproducible ventricular beats were induced.

Results

Noninvasive detection of ventricular arrhythmias before electrophysiologic study: Patient 1 had no premature ventricular beats on 24-hour ambulatory monitor tape recording, and Patient 2 had a total of 1 premature ventricular beat recorded during the 24 hours. Patient 3 had a total of 30 premature ventricular contractions over 24 hours; none were associated with symptoms. No patient had ventricular arrhythmia immediately before or during treadmill exercise testing, although Patient 2 had 10 uniform, fixed coupled premature ventricular contractions during the third minute of postexercise recording. (This patient subsequently underwent repeat treadmill exercise testing after a therapeutic serum concentration of phenytoin was achieved; no premature ventricular beats or VT occurred before, during, or after exercise.)

Electrophysiologic findings: *Baseline intervals:* The baseline surface and intracardiac intervals are listed in Table II. No patient had normal measurements.[23] No specific intracardiac interval consistently was prolonged in each patient, although each patient did have a prolonged QRS duration on the surface electrocardiogram. In addition, 2:1 atrioventricular block within the atrioventricular node occurred in Patient 1 at an atrial pacing rate of 150 beats/min, indicating atrioventricular nodal dysfunction.

Ventricular tachycardia: The basic data are listed in Table III. The rate of the sustained ventricular tachycardia was fast in each patient ranging from 272 to 286 beats/min. The earliest ventricular activation was recorded in each patient by the distal and proximal electrodes on the catheter positioned across the tricuspid valve (Fig. 1 to 3). During sinus rhythm, this catheter recorded low septal right atrial, His, and right ventricular inflow-septal depolarizations (Fig. 1 and 2). In Patients 1 and 2, increased diastolic depolarizations in this right ventricular inflow-septal area during VT provided greater difficulty in determining onset of the depolarization. However, the initial beat of the VT was identifiable (Fig. 1 to 3). Moreover, after procainamide in Patient 1 and after phenytoin in Patient 2, the earliest activation was clearly delineated (Fig. 2 and 3). In each instance, the structure of the QRS in V_1 was of left bundle branch block. No patient had evidence of retrograde ventriculoatrial conduction during either ventricular tachycardia or ventricular pacing at any rate.

The VT was terminated by synchronized direct current cardioversion in Patients 1 and 3 because hypotension-associated symptoms (confusion and chest pain) did not allow time for ventricular stimulation techniques to be used.

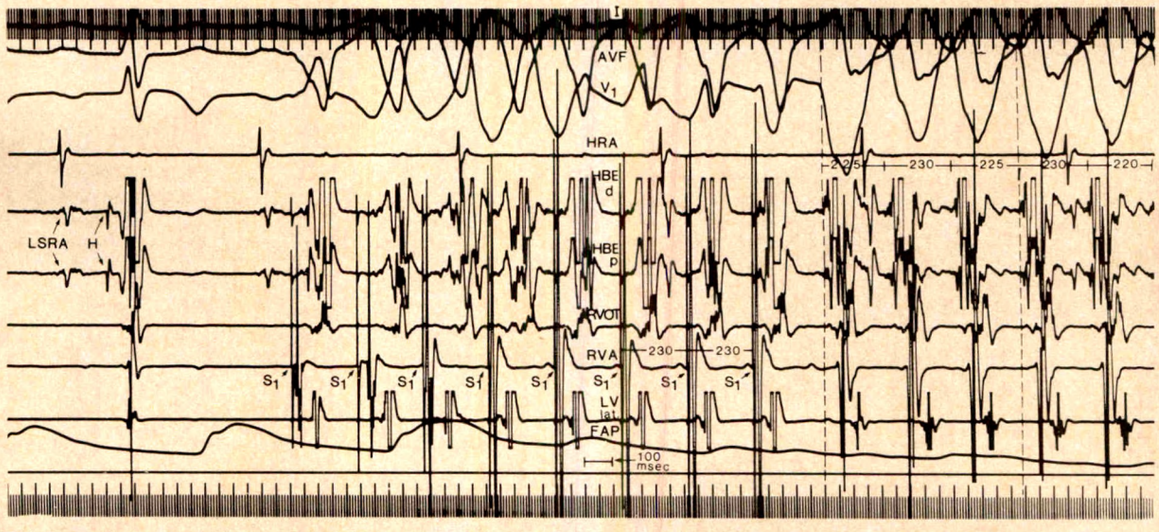

FIGURE 1. Recording of the initiation of VT in Patient 3 before administration of antiarrhythmic agents. After 8 beats of rapid ventricular stimuli (S_1) at 230 ms cycle length, sustained VT is induced at a similar cycle length. The earliest site of activation of the initial beat (**first dashed vertical line**) is recorded by the electrodes which recorded the His potential during sinus rhythm and, therefore, is in the right ventricular inflow-septal area. This activation is unchanged with further beats (for example, shown by the **second dashed line**). The QRS structure is one of left bundle branch block. AVF = surface electrocardiographic lead aVF; FAP = femoral artery pressure; H = His bundle; HBE_d and HBE_p = recording from the distal (d) and proximal (p) pair of electrodes on the His bundle catheter; HRA = high right atrium; I = surface electrocardiographic lead I; LSRA = low septal right atrium; LV lat = lateral left ventricle; RVA = right ventricular apex; RVOT = right ventricular outflow tract; S_1 = ventricular extrastimulus.

Serial drug studies: Electrophysiologic findings: *Intervals:* The changes are listed in Table II.

Ventricular stimulation after phenytoin and propranolol: The findings are listed in Table IV.

Ventricular stimulation after lidocaine, procainamide, and quinidine: Patient 1 was the only patient who underwent repeat electrophysiologic studies after drugs other than propranolol and phenytoin. (After it was found that propranolol prevented and phenytoin did not prevent VT, Patients 2 and 3 did not undergo further serial electrophysiologic studies.) Although the rate was slower, ventricular tachycardia occurred after each of these antiarrhythmia agents. Therapeutic serum concentrations were present after administration of procainamide and quinidine and none were measured after lidocaine. Conversion of VT by ventricular stim-

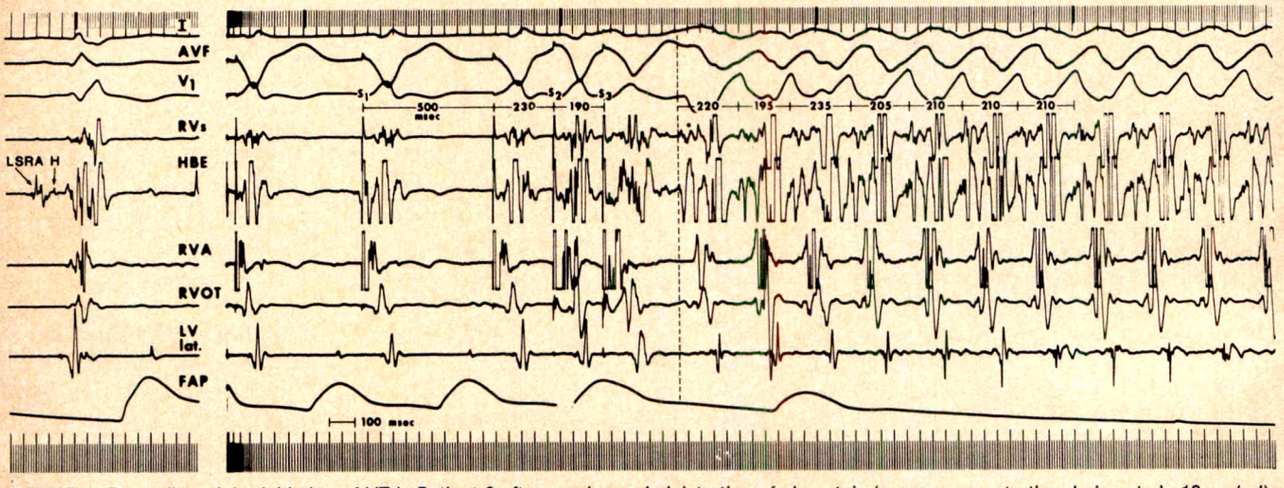

FIGURE 2. Recording of the initiation of VT in Patient 2 after previous administration of phenytoin (serum concentration during study 19 μg/ml). One sinus beat is recorded, then the last 3 beats of 8 beats of ventricular paced rhythm of 500 ms (S_1-S_1) are recorded. After the last S_1, a premature ventricular beat (S_2) is given 230 ms later, followed by a second premature beat (S_3) 190 ms later. Sustained VT is induced at a cycle length of 210 ms. The earliest activation (**vertical dashed line**) is recorded by the 2 catheters recording right ventricular inflow-septal activity: one is by the catheter which has been moved from the high right atrium (lack of ventriculoatrial conduction had been previously noted during baseline study) to the right ventricular inflow-septal area (RVs). This catheter is positioned within 1 cm of the catheter which is recording the low septal right atrial (LSRA), His (H), and right ventricular inflow-septal depolarization during sinus rhythm and, therefore, also is recording the earliest activation during VT. The duration of each ventricular depolarization in this area is long during sinus rhythm and is almost continuous during tachycardia. Left bundle branch block pattern is noted during tachycardia. Abbreviations are as in Figure 1.

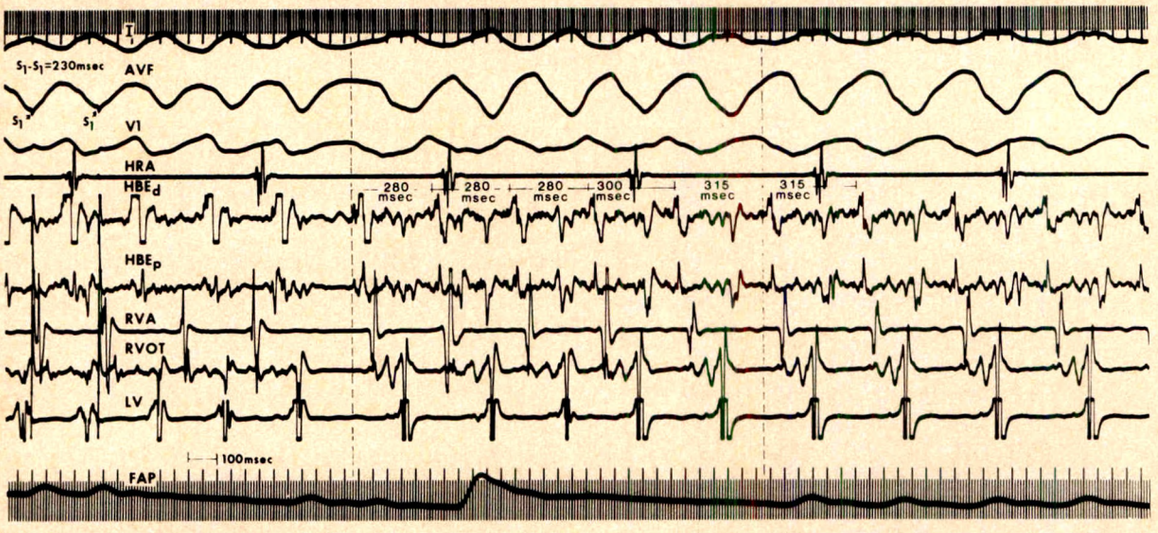

FIGURE 3. Recording of the initiation of VT in Patient 1 after administration of procainamide (serum concentration 7 μg/ml during study). After 8 beats of rapid right ventricular apex pacing (S_1-S_1 230 ms), ventricular tachycardia is induced. After 2 beats that appear to originate from the right ventricular apex, the sustained tachycardia is noted to originate from the right ventricular inflow-septal area because the earliest ventricular activation (**first dashed vertical line**) is recorded by the electrodes on the catheter which recorded the His depolarization during sinus rhythm. The depolarizations from this area are almost continuous. After several beats, the cycle length of the tachycardia lengthens and stabilizes at 315 ms. The earliest activation continues to exist in the inflow-septal area as shown by the **second vertical dashed line.** The QRS complexes are of a left bundle branch structure during the tachycardia. Abbreviations are as in Figure 1.

ulation techniques was unsuccessful after lidocaine, but successful after procainamide and quinidine.

Hemodynamic and angiographic findings (Table V): No patient had normal hemodynamic findings, although Patient 1 only had 2 borderline abnormalities: decreased cardiac index (Fick)[24] and mildly increased right ventricular systolic pressure. Patient 2 had one-half systemic right ventricular systolic pressure, and end-diastolic pressure also was increased. Increased peak systolic and end-diastolic right ventricular pressures were found in Patient 3. The Fick cardiac index was measured before and after propranolol in this patient, and no change was evident (2.02, 2.03 liters/min/m^2, respectively).

Results of treatment: Long-term oral propranolol therapy was initiated in each patient and doses were adjusted to maintain serum concentrations above those obtained during electrophysiologic studies when no VT was induced. Because of induction of sinus and exacerbation of atrioventricular node dysfunction by propranolol, Patient 1 received a permanent ventricular demand pacemaker before dismissal. In the follow-up period (6 to 12 months), each patient has had at least three 24-hour ambulatory electrocardiograms. 2 M-mode echocardiograms, and 1 treadmill exercise test.

Patient 1 has had no adverse effects and each of his noninvasive tests have shown no changes except that during the treadmill test he was able to exercise 1 minute longer compared with his endurance before propranolol. His rhythm remains sinus and he seldom has ventricular paced rhythm at 60 beats/min. His left ventricular function remains good by echocardiogram (shortening fraction unchanged at 40%). The dimensions of his right and left ventricles also are unchanged. Patient 2 also has had no adverse effects. Although the dimensions of her left and right ventricles as well as her shortening fraction are unchanged on echocardiogram, her duration of exercise to exhaustion was shortened by 1.5 minutes compared with baseline values. Patient 3 has had continuation of nonspecific substernal chest pain unrelated to activity or to dysrhythmia as documented by repeat 24-hour ambulatory electrocardiogram and treadmill testing. Rare premature ventricular and atrial beats (average <1 per hour) have been present on several 24-hour electrocardiogram recordings. Her exercise tolerance is essentially unchanged (duration 0.5 minute less than baseline) and her echocardiographic indexes are also unchanged.

Discussion

Several new findings are apparent from this study in 3 adolescents who had undergone surgical repair for tetralogy of Fallot. Despite the absence of significant premature ventricular beats and no VT by noninvasive tests, sustained reproducible VT was induced during electrophysiologic studies. The site of origin was consistently found in the right ventricular inflow-septal area rather than in the outflow tract, and hemodynamic data showed significant right ventricular hypertension in only 1 patient. Propranolol, but not phenytoin, prevented the induction of VT.

Ventricular arrhythmias in patients after repair of tetralogy of Fallot: Depending on the reported series, sudden death in the late postoperative period has accounted for 30 to 75% of late deaths in patients who have undergone repair of tetralogy of Fallot.[1–5] Although some investigators have questioned the association of sudden death with ventricular arrhythmias,[9] many others have reported data to support strongly the hypothesis that premature ventricular beats leading to VT and fibrillation are the likely terminal events in most of these patients.[1–5] Therefore, it is important to detect these ventricular arrhythmias.

TABLE IV Effect of Phenytoin and Propranolol

Patient	Phenytoin (μg/ml)	VT CL (ms)	Induced by (ms)	Terminated by (ms)	Propranolol (ng/ml)	VT
1	22	250	Burst (250)	S_1-S_1 230 (after PA & VT CI 315)	154	...
2	19	210	S_2-S_3 190 (S_1-S_1 500; S_1-S_2 230)	S_1-S_1 250 → VF → defib	49	...*
3	21	240	Burst (230)	DC CV	56	...

* Immediately after propranolol, ventricular tachycardia was induced: 1 burst of 220 ms. Thirty minutes later, without any further drug, no VT could be induced.

DC CV = direct-current cardioversion; defib = defibrillation (direct-current); CL = cycle length; PA = procainamide; S_1-S_1, S_1-S_2, S_2-S_3 (see Table III); VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE V Hemodynamic Data

Patient	RV (mm Hg)	MPA (mm Hg)	PAW (mm Hg)	LV (mm Hg)	Ao (mm Hg)	CI* (liters/min/m^2)
1	40/0,8	25/8 (14)	(7)	100/0,10	100/80 (92)	2.56
2	65/0,12	34/12 (18)†	(14)	...	132/75 (95)	4.54
3	85/0,10	70/15 (35)‡	(9)	100/0,10	100/70 (82)	2.02

Values in parentheses represent mean pressure.

* Calculated by Fick equation (oxygen consumption measured by flow-through technique).

† Right ventricular-main pulmonary artery conduit 80/8 (30).

‡ Right pulmonary artery 28/14 (18).

Ao = aorta; CI = cardiac index; LV = left ventricle; MPA = main pulmonary artery; PAW = pulmonary arterial wedge; RV = right ventricle.

Garson,[11] James,[7] Kavey,[6] and their co-workers have shown that exercise testing is a useful method to detect dysrhythmias in patients who have undergone repair of tetralogy of Fallot. These investigators reported that premature ventricular beats (uniform and multiform) as well as VT were induced during exercise. In the study of Garson et al,[11] the ability to detect ventricular dysrhythmia doubled with exercise compared with resting standard electrocardiogram (30% versus 14% of 104 patients, respectively). In our patients, neither exercise nor surface electrocardiogram (including 24-hour tape recording) were sensitive methods of detecting ventricular dysrhythmias. Based on these data, underlying life-threatening ventricular arrhythmia may not be detected by noninvasive testing.

Intracardiac electrophysiologic studies: Except for the reports by Garson et al[14] and by Vetter and Horowitz,[15] the only other extensive electrophysiologic study in patients who have had VT after repair of tetralogy of Fallot was reported by Horowitz et al.[9] They found that the reentry VT originated from the right ventricular outflow tract in each of their 4 patients. To our knowledge, our study is the first to show VT originating from the right ventricular inflow-septal area in patients who have had repair of tetralogy of Fallot. This likely is near the site of the patch repair of previous ventricular septal defect. Patients 2 and 3 had undergone anterior conduit insertion in the right ventricular outflow tract but activation clearly was later in this area compared with the inflow area. As in the patients in the reports by Horowitz,[9] Josephson,[25] and their co-workers, continuous electrical activity in the area of originating VT was found. Based on this finding as well as on the methods of initiation and termination which were also similar to those of other investigators,[9,18–20,25] the mechanism of the tachycardia appears to be reentry.

Other electrophysiologic findings in our patients were similar to those reported by Gillette et al,[3] and recently by Garson et al[14] and by Vetter and Horowitz[15]: abnormalities were evident throughout the conduction system. Although the hemodynamic data (especially increased right ventricular systolic pressure) were not as consistently abnormal in our patients as they have been reported earlier by Garson et al,[4] perhaps both hemodynamic and conduction system abnormalities are of importance: they may signal underlying ventricular muscle disease, thus predisposing these patients to VT. Because our patients each had undergone repeat intracardiac operations, they may represent a more severe subset of patients who have had repair of tetralogy of Fallot.

Serial drug studies: Before this study, no serial electrophysiologic studies have been reported in tetralogy of Fallot patients who have VT and in whom therapeutic concentrations of phenytoin or propranolol have been achieved. Horowitz et al[9] performed serial drug electrophysiologic studies but each specific drug is not stated. However, they did find that procainamide was successful in preventing induction of VT in 2 of 4 patients. In our study, because propranolol was the only drug that prevented VT in Patient 1, it was used initially in each of the other 2 patients. Further testing with other antiarrhythmic agents was not carried out in these patients because propranolol was found effective. Although Patient 1 had tachycardia induced when a therapeutic procainamide concentration was present, it is possible that if a very high procainamide serum concentration had been achieved, tachycardia may have been prevented.[26,27]

Because of the excellent results in clinical studies reported by Garson,[5,8] Rocchini,[13] and their co-workers, it was unexpected that VT was not prevented by phenytoin. Because Garson et al[5] found serum concentrations of 15 to 20 μg/ml effective in controlling clinical ventricular arrhythmias and because each of our patients had concentrations of ≥19 μg/ml during induction of sustained VT, it is unlikely that too low serum concentrations were achieved in our patients. Neither Garson et al[5,8] nor Rocchini et al[13] carried out electrophysiologic studies in patients taking phenytoin. Therefore, no comparisons can be made regarding inducibility of VT during electrophysiologic studies. It is possible that clinical control of VT by phenytoin does not correlate with control as determined during electrophysiologic studies. Patient 2 in our study did not have premature ventricular beats after the treadmill exercise test, carried out while she was taking phenytoin, and the conclusion may have been made that phenytoin was the drug to choose for long-term therapy. However, because VT again was induced in this patient during electrophysiologic study (when the phenytoin serum concentration was 19 μg/ml), but propranolol was found effective, we chose propranolol as the drug for chronic treatment.

In adult patients, recent data have shown amiodarone is successful in clinically controlling chronic VT.[28,29] However, the effective clinical control does not correlate in many patients with the ease of tachycardia inducibility during invasive electrophysiologic studies.[29] In contrast, data in patients treated with multiple other antiarrhythmic agents have supported the concept of direct correlation between inducibility during electrophysiologic studies and clinical effectiveness.[7–10] To our knowledge, no studies have been reported regarding phenytoin and this relation. We cannot make any conclusions at this point, because our patients had no evidence of clinical VT.

It may be argued that antiarrhythmic treatment is not indicated in patients who have no evidence of clinical VT. Our goal is to prevent sudden death. Based on available data supporting the hypothesis that ventricular arrhythmia is a cause of sudden death in patients who have had earlier repair of tetralogy of Fallot, we believe that treatment should be given if the treatment is well tolerated. The follow-up in these patients shows no exacerbation of preexisting problems as well as no appearance of new problems while receiving chronic propranolol therapy. Longer duration of follow-up is needed, however, before firm conclusions are made.

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Right Ventricular Function in Adults With Pulmonary Hypertension With and Without Atrial Septal Defect

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Using equilibrium (gated) radionuclide ventriculography, right ventricular (RV) function was studied in 22 adults with pulmonary hypertension and in 16 patients without evidence of cardiac disease. To assess the effect of volume overload on RV performance in pulmonary hypertension, RV ejection fractions were compared in patients with and without left-to-right shunts due to atrial septal defect (ASD). In addition, the effect of ASD repair on RV function was examined. In 14 patients with pulmonary hypertension without RV volume overload (group I), the RV ejection fraction (0.35 ± 0.11, mean ± standard deviation [SD]) was significantly lower than in the normal group (0.47 ± 0.11, $p < 0.01$). In 8 patients with left-to-right shunts due to ASD (group II) and with RV systolic pressures similar to those in group I, the mean RV ejection fraction (0.53 ± 0.15) was normal and was significantly higher than in group I ($p < 0.01$). Right ventricular end-diastolic volumes, estimated from combined radionuclide and hemodynamic data, were higher ($p < 0.01$) in group II patients (171 ± 70 ml/m^2) than in group I patients (70 ± 13 ml/m^2). In 5 patients who underwent isolated shunt repair, mean RV ejection fraction decreased postoperatively from 0.57 ± 0.17 to 0.40 ± 0.12 ($p < 0.05$). It is concluded that (1) pulmonary hypertension frequently causes a decrease in RV systolic function due to abnormal afterload; (2) in patients with RV volume overload due to left-to-right shunt, systolic function, as measured by the ejection fraction, remains normal despite pulmonary hypertension, possibly through the Starling mechanism; and (3) RV systolic function often decreases after repair of an ASD.

Abnormally high afterload, or systolic wall stress,[1] may result in depression of ventricular systolic performance. Right ventricular (RV) function has been found depressed in some patients with pulmonary arterial hypertension.[2–4] This depression of systolic performance is probably the direct result of increased afterload, since normal RV contractility has been found in patients with pulmonary hypertension and RV failure.[5,6] Furthermore, RV function often improves after relief of abnormal afterload.[7]

When pulmonary arterial hypertension occurs in the setting of a significant left-to-right shunt due to atrial septal defect (ASD), abnormally high RV afterload and preload may coexist. The manner in which abnormal preload, or diastolic filling, influences the relation between RV afterload and systolic performance has not been defined. Using radionuclide ventriculography, we studied RV function in adults with mild to severe pulmonary arterial hypertension. We compared ejection fractions in patients with and without significant atrial-level left-to-right shunts to assess the influence of abnormal preload in groups with similar degrees of RV systolic hypertension. In addition, we examined the effect of surgical relief of volume overload on RV function in patients with pulmonary hypertension.

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Methods

Subjects: We studied 22 patients with pulmonary arterial hypertension (systolic pressure ≥35 mm Hg) who underwent cardiac catheterization (Table I). Patients with coronary artery disease were excluded. Pulmonary and systemic blood flows were calculated using the Fick method.[8] Group I comprised 14 patients without evidence of RV volume overload. Left-to-right shunts were excluded by oximetry in all. Group II comprised 8 patients with ASD, pulmonary to systemic blood flow ratios of at least 1.8, and RV systolic pressures of at least 35 mm Hg. Group III consisted of 16 control subjects, 8 men and 8 women, ranging in age from 27 to 71 years (mean 51 ± 13), who underwent radionuclide ventriculography. All group III patients underwent cardiac catheterization because of chest pain and were found to have normal coronary arteries, normal hemodynamic features, and normal left ventricular ejection fractions (≥0.50).

Radionuclide studies: Initial radionuclide studies were performed within 1 week of cardiac catheterization except in Patient 15, whose radionuclide examination was performed 2 months after catheterization, but in whom no clinical change had occurred in the interval. Seven of 8 group II patients consented to postoperative repeat radionuclide ventriculog-

TABLE I Clinical, Hemodynamic, and Radionuclide Data

Patient	Age (yr) & Sex	Diagnosis	NYHA Class	RVs (mm Hg)	RA (mm Hg)	PBF (liters/min/m^2)	PVR (dynes s cm^{-5})	MVA (cm^2)	Qp/Qs	RVEF
					Group I: No Shunt					
1	51F	MS, MR	III	37	5	2.7	110	1.4	1.0	0.45
2	75M	MS, MR	III	35	10	2.3	126	1.0	1.0	0.28
3	72F	MS	III	68	8	3.1	178	1.6	1.0	0.43
4	65M	MS	III	72	5	1.9	416	0.3	1.0	0.31
5	65F	MS	IV	36	5	1.1	400	0.4	1.0	0.58
6	75F	MS, MR	III	36	6	2.5	64	0.8	1.0	0.22
7	50F	MS, MR, AR	III	46	8	3.9	39	1.2	1.0	0.31
8	73F	MS	III	47	9	1.9	148	0.6	1.0	0.42
9	57F	MS	III	48	4	3.5	74	1.1	1.0	0.35
10	69F	MS	III	90	13	1.7	615	0.3	1.0	0.43
11	62M	COPD	III	60	5	3.5	394	...	1.0	0.45
12	26F	PPHT	III	81	15	2.1	930	...	1.0	0.28
13	29F	PPHT	III	110	11	1.2	2,926	...	1.0	0.30
14	28M	VSDR	IV	71	19	1.0	2,322	...	1.0	0.14
Mean	57	...	...	60	9	2.3	624	...	1.0	0.35
SD	18	...	...	23	4	0.9	891	...	...	0.11
					Group II: Left-to-Right Shunt					
15	31F	2° ASD, PAPV	III	100	5	3.2	735	...	1.9	0.65
16	64M	2° ASD	II	40	10	9.0	62	...	4.2	0.56
17	73F	2° ASD	III	43	10	4.4	169	...	2.9	0.61
18	46F	2° ASD	II	42	10	11.4	74	...	3.5	0.79
19	66F	2° ASD	III	90	18	8.0	196	...	3.5	0.41
20	69F	2° ASD	III	35	5	7.9	98	...	2.4	0.39
21	63F	2° ASD, MS	III	55	8	8.6	101	1.4	4.2	0.48
22	57M	1° ASD, PS	II	75	16	5.7	83	...	2.7	0.37
Mean	59	...	...	60	10	7.3	190	...	3.2	0.53
SD	14	...	...	25	5	2.7	225	...	0.8	0.15

AR = aortic regurgitation; 1° ASD = ostium primum atrial septal defect; 2° ASD = ostium secundum atrial septal defect; COPD = chronic obstructive pulmonary disease; MR = mital regurgitation; MS = mitral stenosis; MVA = mitral valve area; NYHA = New York Heart Association; PAPV = partially anomalous pulmonary venous return; PBF = pulmonary blood flow; PPHT = primary pulmonary hypertension; PS = pulmonary stenosis; PVR = pulmonary vascular resistance; Qp/Qs = pulmonary to systemic blood flow ratio; RA = mean right atrial pressure; RVEF = right ventricular ejection fraction; RVs = right ventricular systolic pressure; VSDR = status after ventricular septal defect repair.

raphy. Five patients were studied 4 to 8 days after surgery, and 2 patients were studied 2 months (Patient 20) and 4 months (Patient 15) after surgery.

Red blood cells were labelled in vivo by intravenously injecting unlabelled stannous pyrophosphate (5 mg Pyrolite, New England Nuclear, Boston, Massachusetts) followed by 15 to 25 mCi of technetium-99m as pertechnetate 15 to 20 minutes later.[9] Gated radionuclide ventriculograms were obtained with an Anger scintillation camera and a high-sensitivity straight-bore, 30° slant-hole collimator (Engineering Dynamics, Lowell, Massachusetts), using a previously described technique.[10] Using a modified left anterior oblique projection (30° caudal tilt), 10 million counts were acquired in a 64 × 64 matrix mode on magnetic disk (PDP 11/34 and Gamma-11 system, Digital Equipment, Maynard, Massachusetts). Data acquisition was physiologically gated to the patient's electrocardiogram, with the cardiac cycle divided into 25 ms frames.

Right ventricular ejection fractions were measured by a method similar to that of Slutsky et al.[11] A preliminary RV region-of-interest was manually drawn on the end-diastolic frame, using a computer joy-stick. A preliminary RV frame-activity curve was generated, permitting selection of end-diastolic and end-systolic frames. A stroke volume image, derived by computer subtraction of the end-systolic from the end-diastolic frame, depicted the ventricular regions, and a paradox image, derived by computer subtraction of the end-diastolic from the end-systolic frame, depicted atrial regions.[12,13] A summation of the stroke volume and paradox images, which aided in delineating the right atrioventricular plane, was used to redraw the RV region-of-interest, if necessary (Fig. 1). A 3-pixel wide background region was drawn immediately adjacent to the RV region (Fig. 1). At its superior margin, the background region was adjacent to the RV outflow tract. It extended along the lateral and inferior RV borders, but not the interventricular septum. Background was subtracted using counts/pixel in the background region at the end-systolic frame, and the ejection fraction was calculated as (EDC − ESC)/EDC, where EDC and ESC are background-corrected RV end-diastolic and end-systolic counts, respectively. We have found excellent correlation between this method of calculating RV ejection fraction and the first-pass method of Tobinick et al[14] (r = 0.91) in a group of 30 patients, including patients with RV dilatation due to valvular or congenital heart disease, pulmonary disease, or cardiomyopathy. Intraobserver correlation was excellent (r = 0.98, standard error of the estimate = 0.04). For those patients in whom the heart rate during radionuclide study was within 10% of the heart rate during catheterization, RV end-diastolic volume (EDV) was estimated from pulmonary blood flow (PBF) and heart rate (HR) measured during catheterization: RVEDV (ml/m^2) = [PBF (ml/min/m^2)]/[HR (min^{-1}) × RV ejection fraction] (Equation 1).

The ratio of right-to-left ventricular end-diastolic counts was used to estimate postoperative changes in relative ventricular end-diastolic volumes. Background-corrected RV end-diastolic counts were calculated as described above. The end-diastolic left ventricular perimeter was drawn manually, and the left ventricular background regions were defined automatically using a previously described computer algorithm.[12] The left ventricular region was redrawn, if necessary, on an ejection fraction image,[12] and background regions were redefined as before. Background was subtracted using average counts/cell in the background regions at the left ventricular end-systolic frame, and left ventricular end-diastolic counts was calculated.

Statistical methods: Comparisons of RV ejection fractions and of hemodynamic data in the 3 patient groups were made

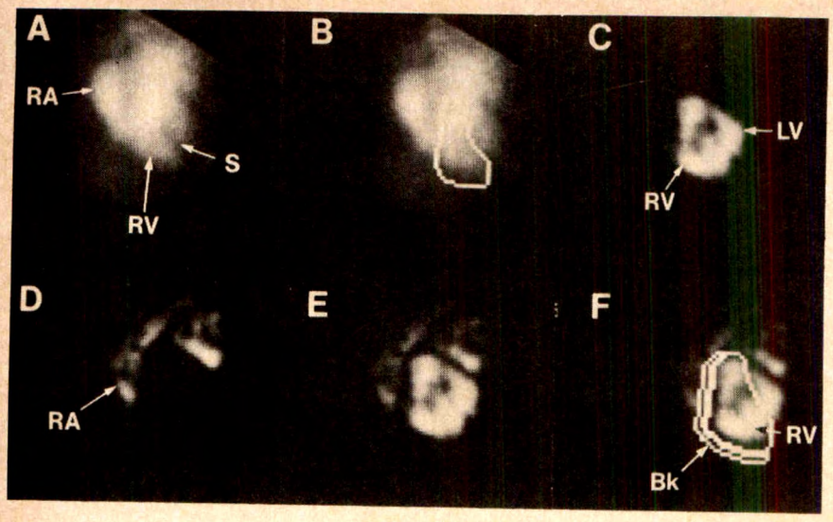

FIGURE 1. A, preliminary end-diastolic image. RA = right atrium; RV = right ventricle; S = interventricular septum. **B,** preliminary RV region-of-interest. **C,** stroke volume image derived by computer subtraction of end-systolic frame from end-diastolic frame. LV = left ventricle. **D,** paradox image derived by computer subtraction of end-diastolic from end-systolic frame. **E,** computer summation of stroke volume and paradox images. **F,** final RV and background (Bk) regions-of-interest.

using 1-way analysis of variance.[15] When the hypothesis of equal treatment means was rejected, the contrast method of Scheffe[16] was used to determine the proportional contribution of each patient group to the overall effect on the analysis of variance. In addition, significant contributions to the variance were examined using 2 sample t tests. Preoperative and postoperative radionuclide measurements were compared using the paired t test.

Results

Hemodynamic data are presented in Table I. Right ventricular systolic pressures were similar in groups I (average 60 ± 23 mm Hg [SD]) and II (average 60 ± 25 mm Hg). Patient 22 had pulmonary stenosis with a 24 mm Hg peak-to-peak pulmonary valve gradient. In group I, pulmonary vascular resistance averaged 624 ± 891 dynes s cm^{-5}. In group II, pulmonary vascular resistance averaged 190 ± 225 dynes s cm^{-5}, although the difference from group I was not statistically significant using either parametric or distribution-free analysis. Each group II patient had a significant step-up in oxygen content (≥2.0 ml/100 ml) between mixed venous and right atrial blood samples, with the ratio of pulmonary to systemic blood flow ranging from 1.9 to 4.2 (mean 3.2 ± 0.8).

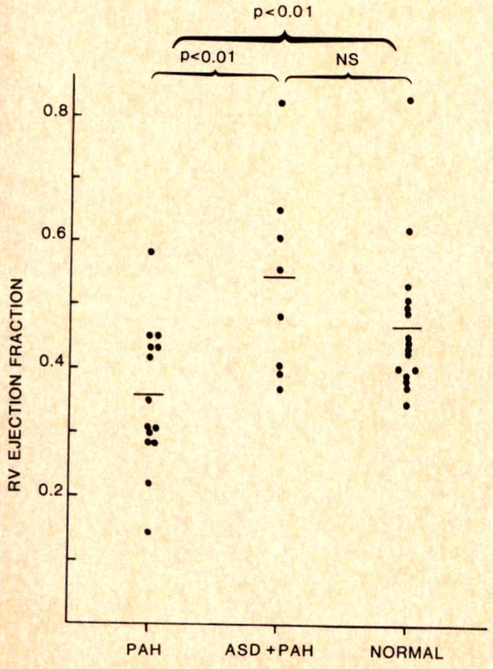

FIGURE 2. Comparison of right ventricular (RV) ejection fractions in patients with pulmonary arterial hypertension (PAH) without left-to-right shunt, in patients with pulmonary arterial hypertension and left-to-right shunt through an atrial septal defect (ASD), and in normal subjects.

Radionuclide data: In the group without evidence of cardiac disease (group III), RV ejection fractions averaged 0.47 ± 0.11 (Fig. 2). In group I, RV ejection fractions averaged 0.35 ± 0.11. In patients with ASD (group II), RV ejection fractions ranged from 0.37 to 0.79 (mean 0.53 ± 0.15). Mean RV ejection fractions were significantly different in the 3 groups ($p < 0.01$). According to the Scheffe contrast method, the significant contributors to this difference ($p < 0.05$) were, in order, group I versus II, group I versus II and III, and group I versus III. In 7 group I patients and 5 group II patients in whom heart rate during catheterization was within 10% of heart rate during radionuclide study, RV end-diastolic volumes were estimated by combining radionuclide and hemodynamic data according to equation 1. RV end-diastolic volumes were significantly larger ($p < 0.01$) in group II (171 ± 70 ml/m^2) than in group I (70 ± 13 ml/m^2).

All 8 group II patients underwent surgical repair of the ASD. Patient 15, with severe preoperative pulmonary hypertension, developed severe RV failure immediately after surgery, requiring isoproterenol and nitroprusside infusions for 4 days. The patient's condition subsequently improved and she was discharged on the 13th postoperative day. The remaining 7 patients had uneventful early postoperative courses. Two to 14 months postoperative follow-up demonstrated clinical improvement in all group II patients except Patient 22, in whom repeat catheterization 14 months after surgery showed a residual ASD with a pulmonary to systemic

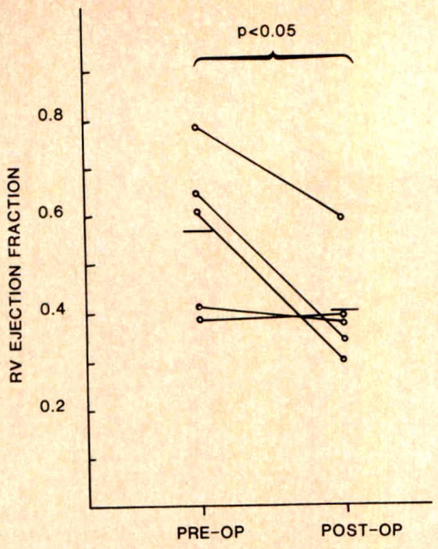

FIGURE 3. Comparison of preoperative (PRE-OP) and postoperative (POST-OP) right ventricular (RV) ejection fractions in patients who underwent isolated repair of atrial-level left-to-right shunts.

blood flow ratio of 1.5 and RV systolic pressure of 50 mm Hg.

Seven group II patients consented to repeat postoperative radionuclide ventriculography. In all 5 group II patients studied who underwent isolated ASD repair, postoperative RV ejection fractions decreased or remained unchanged compared with preoperative values (Fig. 3), with a mean decrease from 0.57 ± 0.17 to 0.40 ± 0.12 ($p < 0.05$). Right ventricular ejection fraction increased postoperatively in Patient 21 (0.48 to 0.64), who underwent replacement of a stenotic mitral valve and in Patient 22 (0.37 to 0.43), who underwent valvulotomy for pulmonic stenosis in addition to ASD repair.

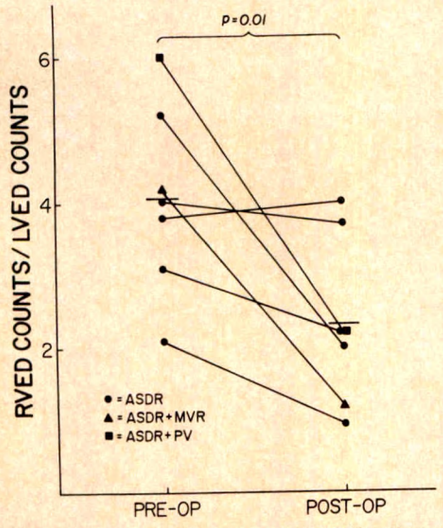

FIGURE 4. Comparison of preoperative (PRE-OP) and postoperative (POST-OP) ratios of right ventricular (RVED) to left ventricular (LVED) end-diastolic counts in patients who underwent ASD repair (ASDR). MVR = mitral valve replacement; PV = pulmonary valvulotomy.

The ratio of right-to-left ventricular end-diastolic counts decreased postoperatively from 4.1 ± 1.3 to 2.3 ± 1.2 ($p = 0.01$), indicating a postoperative decrease in RV end-diastolic volume, an increase in left ventricular end-diastolic volume, or both (Fig. 4 and 5).

Discussion

Our study indicates that RV systolic function, as assessed by the ejection fraction, is frequently depressed in adults with chronic pulmonary arterial hypertension. Since variables of RV performance which are relatively independent of afterload, such as the maximal rate of isovolumic pressure increase, are normal or elevated in chronic pulmonary hypertension,[5,6] depressed systolic function probably results directly from abnormally high systolic wall stress, rather than from depressed contractility. In patients with pulmonary hypertension and significant left-to-right shunts, our finding of normal RV ejection fractions suggests that the volume overloaded right ventricle maintains normal systolic function, despite increased afterload. After surgical repair of ASD in patients with pulmonary hypertension, RV function often declines.

Ventricular afterload, or systolic wall stress, is directly proportional to systolic pressure but is also related directly to chamber dimension and inversely to wall thickness.[1] Differences in chamber dimension and wall thickness probably account for much of the variability in RV performance which has been reported in the presence of pressure overload. Children with isolated pulmonic stenosis, who have severe RV hypertrophy, have been found to have normal or increased RV ejection fractions,[17,18] whereas in adults with pulmonary hypertension due to valvular heart disease or obstructive lung disease, RV ejection fractions have been found

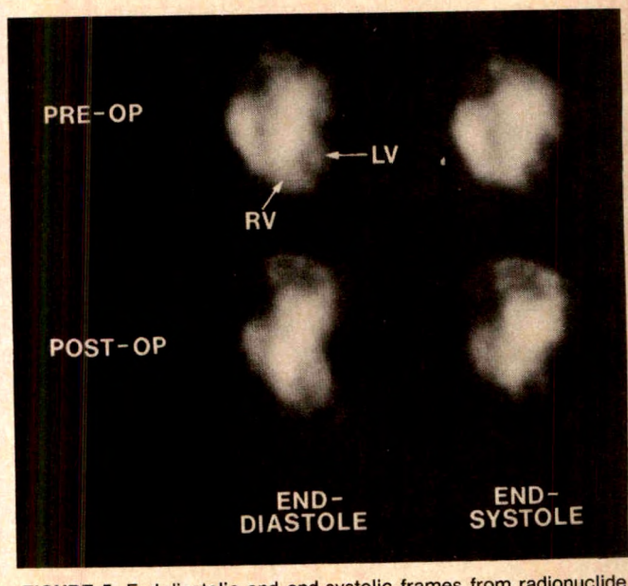

FIGURE 5. End-diastolic and end-systolic frames from radionuclide ventriculograms performed before and after ASD repair and mitral valve replacement in Patient 21. The postoperative study shows reduction in the volume of the previously dilated right ventricle (RV). LV = left ventricle.

to be variably depressed.[2–4] The depressed RV ejection fractions found in our group I patients are likely to be due to abnormal systolic pressure in the absence of adequate compensatory hypertrophy.

In contrast to group I, all of our group II patients with ASDs and predominant left-to-right shunts had normal RV ejection fractions despite pulmonary hypertension. The best explanation for this finding is that systolic performance was normalized by increased preload due to left-to-right shunting. This conclusion is supported by the larger RV end-diastolic volumes in group II and by the decrease in RV ejection fractions after ASD repair. Two additional explanations for the normal RV ejection fractions in group II must be considered. First, contractility may have been increased. This possibility is unlikely since chronic volume loading would be expected to depress contractile function. Secondly, systolic wall stress might have been normalized despite pulmonary hypertension. In group I, the development of pulmonary hypertension may have been insidious, with onset in early life, permitting greater degrees of RV hypertrophy. This increased wall thickness may have resulted in normalization of RV systolic wall stress and greater RV ejection fractions for the same degree of systolic pulmonary hypertension in group II compared with group I, in which pulmonary hypertension may have occurred later in life and more rapidly.

It has been suggested that the chronic volume load imposed by a left-to-right shunt may result in deterioration of RV systolic function.[19,20] Liberthson et al[19] found evidence of RV dysfunction in over half of their adult patients with ASD. However, in most of their patients, Liberthson et al assessed RV function subjectively. They employed a left anterior oblique view without caudal angulation, in which the overlap between the RV and the dilated right atrium is greater than in the caudally tilted view. Furthermore, in most cases they recorded images only at "end-systole" and "end-diastole." These intervals may not have coincided with the timing of peak and trough RV volumes, particularly in the presence of an RV conduction delay, which may accentuate the difference in timing between right and left ventricular end-systole. Both the greater overlap between right ventricule and right atrium, and the potential error in choosing RV end-systole, may result in underestimation of RV systolic function. From our findings, it is likely that patients in group II had some reduction in RV contractility, as evidenced by the decrease in the ejection fraction after surgical reduction in preload. However, our data do not support the contention that RV dysfunction due to chronic volume overload is a major problem in adults with ASD and significant left-to-right shunts.

Our finding of a reduction in RV ejection fraction postoperatively in the patients who underwent isolated ASD repair probably reflects a decrease in preload. Although a decrease in RV function resulting from myocardial ischemia during cardiopulmonary bypass cannot be excluded, our patients were restudied at least 4 days after surgery, at which time ischemic decrease in ventricular function would no longer be expected.[21,22] Postoperatively, RV ejection fraction increased in 1 patient who underwent mitral valve replacement for mitral stenosis and in 1 patient who underwent valvulotomy for pulmonic stenosis in conjunction with ASD repair. The effect of reduced RV afterload by these procedures may have outweighed the effect of preload reduction. The postoperative courses in our patients were similar to those described in previous studies, indicating the surgical repair of ASD in adults is safe and often produces clinical improvement.[19,23,24] In most patients, the postoperative decrease in RV ejection fraction was not sufficient to alter the clinical course adversely.

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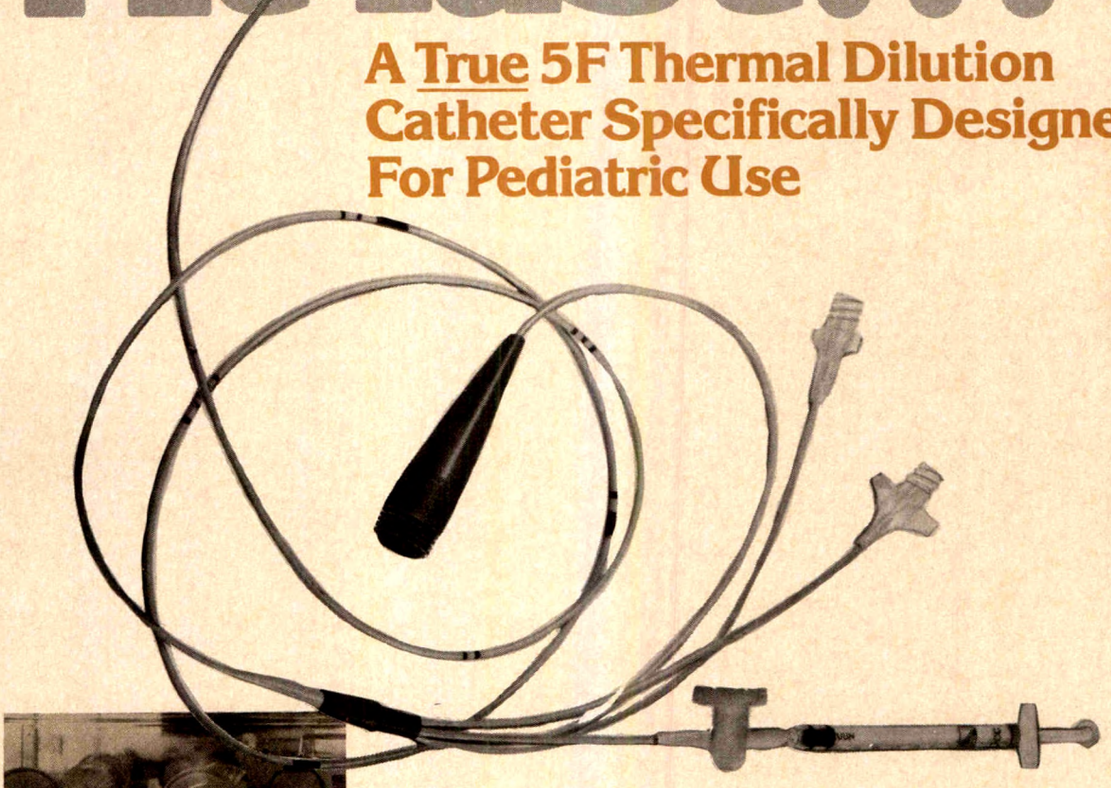

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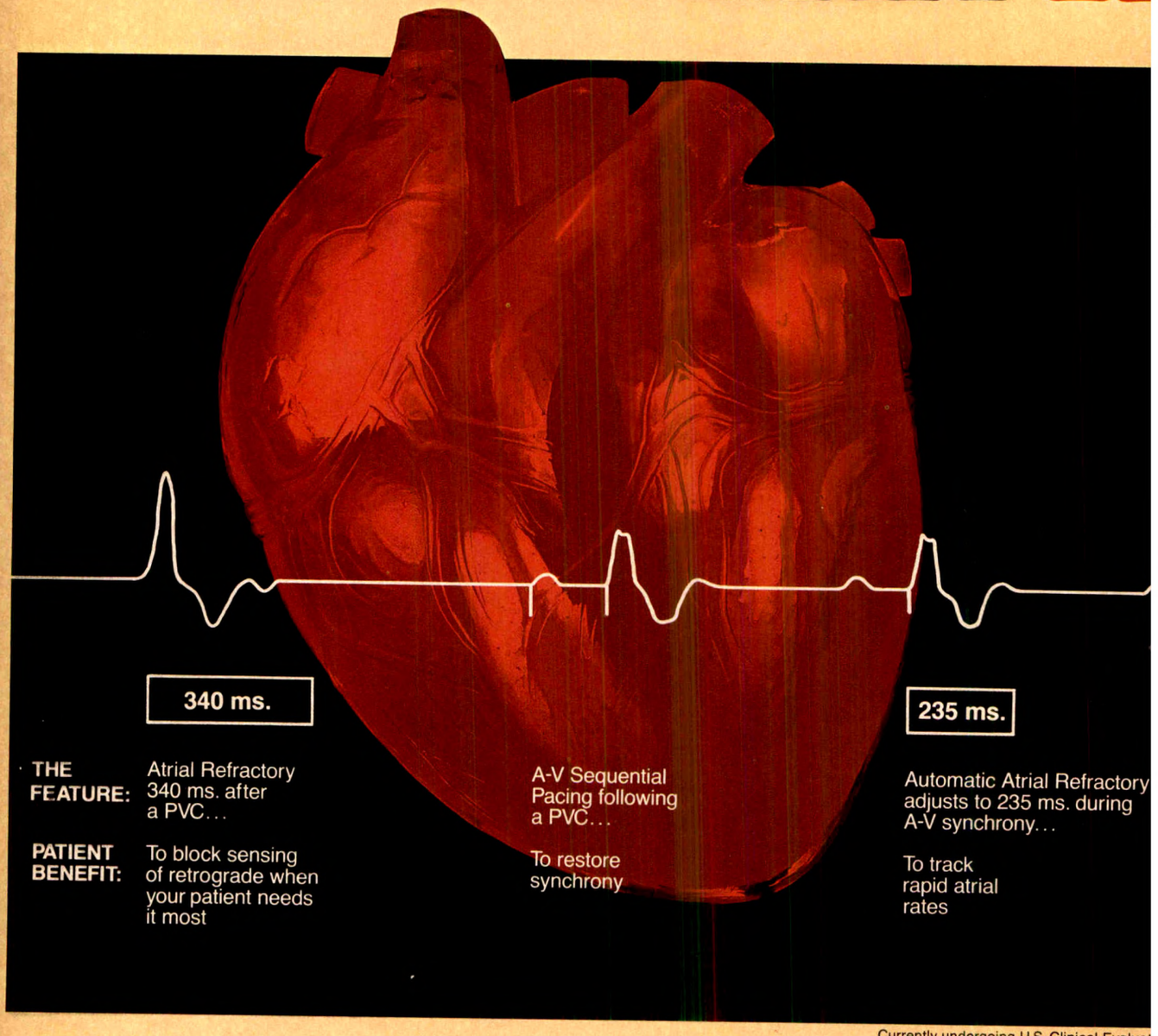

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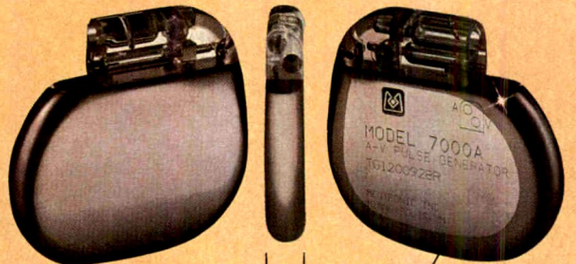

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Intended Use

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With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

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Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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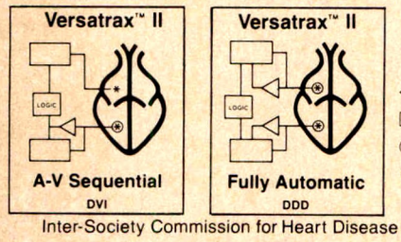

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□ = Output Circuit
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Edited by Michael H. Grieco, M.D.
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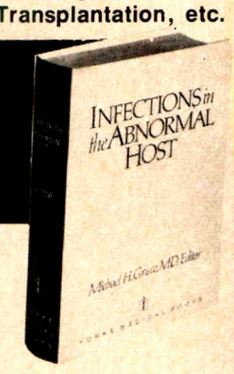

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BASIC THERAPY FOR THE PREVENTION OF ANGINA PECTORIS*

Report from "Step-Care Therapy for Ischemic Heart Disease"
—a special symposium preceding the annual meeting
of the American College of Cardiology, April 24, 1982.

Synopsis of the Symposium

Step 1: Nitrates

Since nitrates both reduce myocardial oxygen demand and increase myocardial oxygen supply, their use is warranted as initial therapy for the control of angina pectoris. Dosage needs often vary significantly from patient to patient, and attention should be given to ensure that an adequate dosage level has been established.

Step 2: Nitrates and beta blockers

For angina refractory to maximum-dose nitrate therapy, the complementary actions of beta blockers and nitrates provide a rational therapeutic modality. At this point a beta blocker should be added to the nitrate regimen.

Step 3: Nitrates and calcium antagonists

Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

Nitrates are basic in step-care therapy for ischemic heart disease

Step 1
Stable or unstable angina: Nitrates

Step 2
If not controlled: Nitrates + beta blockers

Step 3
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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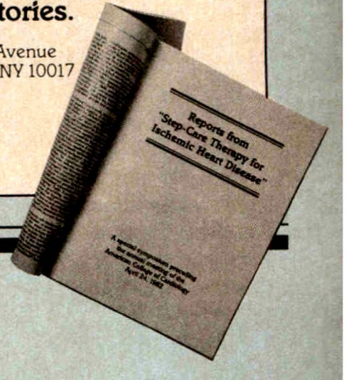

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The Univentricular Heart: Combined 2-Dimensional–Pulsed Doppler (Duplex) Echocardiographic Evaluation

GEORGE S. BISSET, III, MD and STEPHEN S. HIRSCHFELD, MD

Two-dimensional echocardiographic-pulsed Doppler (2D-PD) evaluation was performed in 14 patients with a univentricular heart. Accurate information on ventricular structure, atrioventricular valve status, and great vessel anatomy and function was obtained. The characteristic morphologic features were verified in each case by angiography or autopsy, or both. In several patients, 2D-PD evaluation provided more accurate anatomic and functional information than did cardiac angiography in standard views, particularly with regard to atrioventricular valve function. Four children with pulmonary atresia and 4 with pulmonary stenosis were identified prospectively. No patient had 2D-PD evidence of aortic obstruction. Four children had typical 2D-PD patterns consistent with atrioventricular valve regurgitation. Thus, 2D echocardiography coupled with a range-gated Doppler system will improve recognition of patients with a univentricular heart and permit thorough evaluation of specific anatomic details.

With the introduction of improved surgical procedures in patients with a univentricular heart, accurate preoperative assessment has become essential. Anatomically and morphologically, these children may be difficult to evaluate, particularly in the neonatal period. Complex great vessel positions, the presence or absence of pulmonary or aortic stenosis, or both, and the contribution of a patent ductus arteriosus need to be recognized before planning long-term medical management. In the mid-1970s, several reports discussed M-mode echocardiographic features of the univentricular heart.[1–5] However, adequate surgical planning could not be undertaken on the basis of M-mode echocardiography alone.

Recently, 2-dimensional (2D) or cross-sectional echocardiographic techniques have provided more anatomic information on patients with univentricular heart,[6–8] but little functional data. More recently, 2D or cross-sectional echocardiographic techniques have been combined with range-gated pulsed Doppler (PD) to obtain specific anatomic and hemodynamic information.[9,10] Ventricular and atrial structure, atrioventricular (AV) valve connections, and great vessel relations have been visualized with use of 2D techniques.[6,11,12] With PD, additional information can be gained on pulmonary and aortic flow patterns,[13,14] AV valve competence,[15,16] and patterns of shunts.[17–19] No reports on the use of PD techniques in patients with univentricular heart have appeared.

The present report is a combined 2D echocardiographic-pulsed Doppler evaluation of 14 patients with a univentricular heart. The group includes all those patients whose heart demonstrated absence of the ventricular septum, as defined by Anderson et al.[20,21] Each patient underwent cardiac catheterization with selective angiography. Investigation was undertaken to evaluate the ability of the 2D-PD system to predict accurate information on AV valve structure and function, ventricular structure, and great vessel positions and flow patterns in children with a univentricular heart.

Definitions and Terms

Functional single ventricle-univentricular heart (terms used interchangeably): The definition of single ventricle is controversial.[21–23] We have chosen to accept the interpretation of Anderson et al,[20] who describe the univentricular heart as one in which the posterior ventricular septum is absent. Atresia of an AV valve, common AV valve, and straddling AV valve are included in this definition. These patients may or may not have ventricular outflow chambers.

Outflow chamber: This is a small infundibular chamber that communicates with the larger, main ventricle and is partially separated from it by the bulboventricular ridge, rather than the true ventricular

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septum. This outflow chamber may not entirely encompass an AV valve anulus and may be in a noninverted (rightward) or inverted (leftward) position.

Atrioventricular valves: The AV valves are described as right-sided or left-sided, the right being anterior and the left being posterior. A common AV valve is defined as one that is single and midline, without commitment to the right or left.

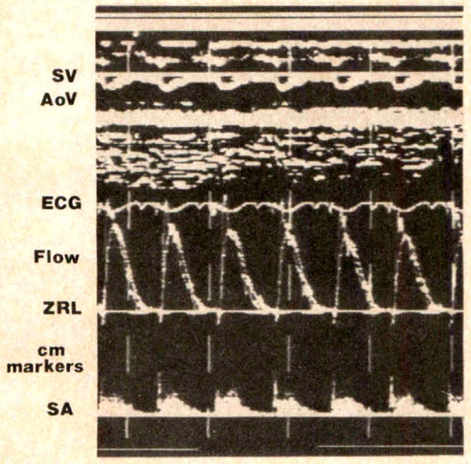

FIGURE 1. Standard display of pulsed Doppler echocardiographic tracing recorded at the level of the aortic valve (AoV). At the top is a compact M-mode echocardiogram. The sample volume (SV) is positioned in the aortic root. Below the M-mode tracing is an electrocardiographic rhythm strip (ECG). The spectral flow velocity is demonstrated as a series of dots arranged (in this example) in a linear pattern, indicative of laminar flow. Flow directed toward the transducer is indicated by deflection above the zero reference line (ZRL). The Doppler signal amplitude (SA) indicates the strength of the flow signal detected by the spectral processor. This tracing demonstrates normal, nonturbulent, aortic flow. Cm markers = 1 cm markers; flow = spectral velocity flow patterns.

Great vessel relationships: The vessels were defined as normally positioned, D-transposed, or L-transposed. The prefixes D and L refer only to the relative rightward or leftward positions of the aorta and provide little valuable morphologic data.

Methods

Fourteen patients, 6 boys and 8 girls, with presumed single ventricle underwent 2D echocardiography and PD analysis. Their ages were 1 day to 19 years (mean 5 years), and 7 (50%) were less than 6 months of age.

In each patient the diagnosis of single ventricle was established at cardiac catheterization. Seven patients underwent ultrasound examination before angiography. Of the remaining 6 patients, 2 were catheterized elsewhere and angiograms were not viewed before echocardiographic study. The other 4 patients underwent cardiac catheterization at this institution several years before the noninvasive studies. In 2 patients, autopsy results confirmed the cardiac diagnosis.

Ultrasound examinations were performed with the ATL Mark V System (Advanced Technology Laboratory, Bellevue, Washington), a self-contained echocardiography/Doppler duplex ultrasound system that permits sector-type, real-time visualization of cardiac images and frozen-frame evaluation of blood flow characteristics on the image, using PD techniques. We used a 5 MHz stationary rotor scan head with a receiver frequency response of 1 to 8 MHz broadband. Spectral and audio Doppler signals provided flow velocity information from a 2 by 4 mm Doppler sample volume. With range gating, this Doppler sample volume could be positioned anywhere along a continuously variable M-mode line, with a maximal depth of 9 cm. An M/Q display of the Doppler spectrum was recorded from the echocardiographic oscilloscope (315A Video Display) (Fig. 1). In the upper portion of the display the M-mode echocardiogram is visualized, with a superimposed line indicating the Doppler sample volume location. Below this display is the simultaneously recorded electrocardiogram. The lower half of the format reveals the spectral flow velocity pattern and the Doppler signal amplitude. Flow toward the transducer is represented by dis-

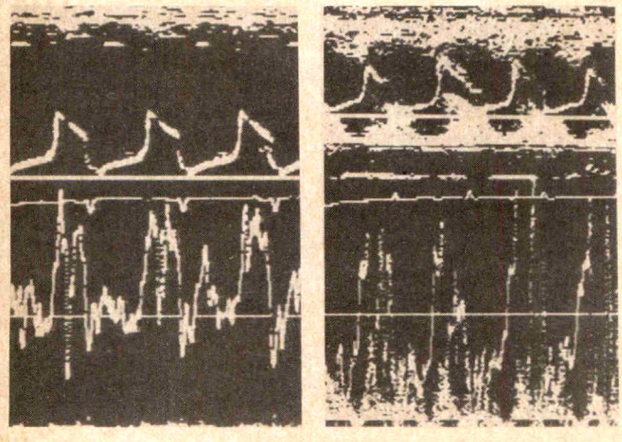

FIGURE 2. Atrioventricular valve competence as demonstrated in an apical view. A 2D apical view of the heart was used with localization of the Doppler sample volume within the mitral anulus. The same view was used to detect tricuspid valve insufficiency. **Left,** normal mitral flow is indicated by nonturbulent flow directed toward the transducer during ventricular diastole. Little flow is detected during ventricular systole. **Right,** mitral insufficiency is demonstrated by noting turbulent flow directed away from the transducer during ventricular systole.

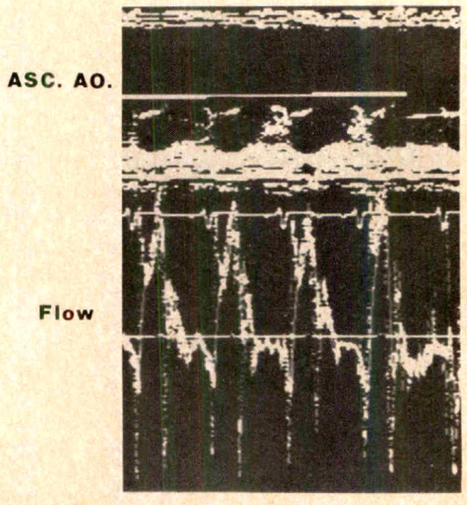

FIGURE 3. Demonstration of Doppler flow in the aortic root. Normal aortic flow pattern from suprasternal notch view. Laminar flow is directed toward the transducer during systole. ASC. AO = ascending aorta.

placement of the histogram above the baseline, and flow away from the transducer by displacement below the baseline. Turbulent flow is demonstrated by dispersion of the time interval histogram, whereas coherence of the pattern suggests laminar flow.

The patients were examined in the supine position with the transducer initially in the third or fourth intercostal spaces along the left sternal border. Long- and short-axis views of the ventricles and great vessels were obtained. Acoustic windows in the apical, subxiphoid, and suprasternal notch areas were also used in each patient to visualize various structures. The method for obtaining these views was previously described.[6] PD examinations were attempted in positions in which the flow was least perpendicular to the Doppler sample volume, so as to maximize the opportunity of detecting the optimal Doppler signal. Evaluation of the histograms was qualitative, as no attempt was made to quantitate flow volumes.

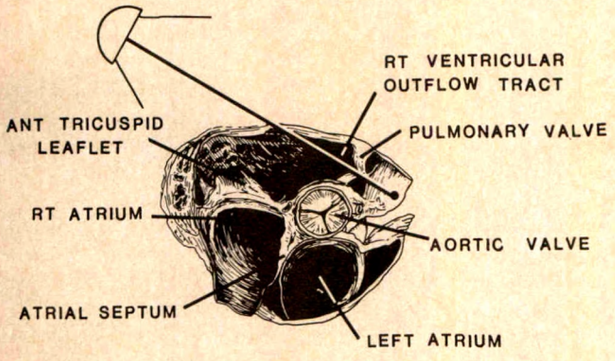

FIGURE 4. Placement of the Doppler sample volume (**black dot**) in the main pulmonary artery. The short-axis view maximizes the ability to detect laminar or turbulent flow. ANT = anterior; RT = right.

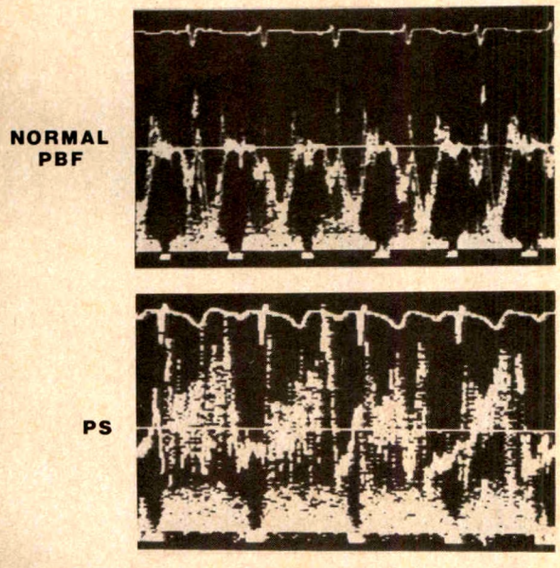

FIGURE 5. Top, laminar flow pattern demonstrated in the main pulmonary artery in a patient with catheterization-proven normal pulmonary blood flow (PBF). **Bottom,** the time interval histogram of a patient with pulmonary stenosis (PS) reveals a widely dispersed dot pattern consistent with turbulent systolic flow.

To evaluate AV valve status, an apical 4-chamber view was used (Fig. 2). The Doppler sample volume was positioned in the left atrium (or common atrium) and subsequently in the right atrium just proximal to the AV valve. This position approximated the center of the valve ring. The Doppler recordings were initially performed in this position and then the Doppler sample volume was moved more proximally and from side-to-side in the atrium in attempts to localize a regurgitant stream. Any turbulent flow directed below the baseline during systole was defined as AV valve insufficiency.

PD examinations also were performed to evaluate flow patterns in the aortic and pulmonary outflow tracts (Fig. 3 and 4). Suprasternal notch and long- and short-axis views were optimal for performance of these studies. The Doppler sample volume was initially positioned just distal to the valve and then advanced through the valve to a more proximal position in the outflow tract. In patients with unobstructed pulmonary blood flow, typical laminar histograms were obtained and were associated with a smooth audio signal (Fig. 5). Patients with aortic or pulmonary stenosis demonstrated normal flow patterns proximal to the obstruction and turbulent flow, with a rough audio signal distal to the obstruction. Children with patent ductus arteriosus had Doppler continuous flow patterns in the pulmonary trunk. If pulmonary atresia was present, no flow was demonstrated proximal to the pulmonary valve, and ductal or surgically created shunt flow patterns were visualized distal to the valve. This pattern has been described previously by Korfhagen et al.[24]

Results

Ventricular structure: In each of the 14 patients, the 2D-PD examination was accurate in predicting ventricular structure (Table I). Nine patients had findings consistent with single ventricle of the left ventricular type, that is, the outflow chamber, as identified by the bulboventricular ridge, was directed toward the right and anterior.[25] In 2 patients the outflow chamber was left-sided and anterior, suggesting ventricular inversion. The great vessels were L-positioned, lending further credence to the diagnosis of inversion. The remaining patient with ventricular inversion demonstrated dextrocardia with a large, smooth-walled, right-sided chamber and a small, anterior, leftward

TABLE I Distribution of Cases

Diagnosis	n
SV with outflow chamber	12
Ventricular status	
Without ventricular inversion	9
With ventricular inversion	3
Great vessel status	
Normal	5
D-transposed	4
L-transposed	3
AV valve status	
Two AV valves	6
Small right-sided valve	6
Right-sided atresia	2
Left-sided atresia	1
Single (common) large valve	3
SV without outflow chamber	2
Great vessel status	
L-transposed	1
D-transposed	1
AV valve status	
Single (common) AV valve	2

AV = atrioventricular; SV = single ventricle.

outflow chamber giving rise to the aorta. In the 2 patients with undifferentiated single ventricles, no outflow chamber was identified, that is, no bulboventricular ridge could be identified. Angiography confirmed this finding.

Atrioventricular valves: Six patients had 2 AV valves demonstrated. In every case, the right-sided valve appeared to be approximately one-fifth to one-third the size of the left-sided valve (Fig. 6). One child with a straddling, small dysplastic right-sided AV valve demonstrated regurgitation of the valve on Doppler examination.

Two children had thickened, ultrasound-dense membranes in regions where normal right-sided AV valves were developmentally expected. Another child had the same plate-like density on the left side (Fig. 7). No patient had AV valve regurgitation.

Of the 5 children with single, uncommitted AV valves, the 3 with outflow chambers had evidence of AV valve regurgitation on Doppler examination, which was confirmed at cardiac catheterization. At autopsy, 1 of these 3 had a rudimentary right ventricular outflow tract and a large dysplastic AV valve typical of an endocardial cushion defect.

Great vessel relationships and flow patterns: Five patients in the group had a normal "ball and sausage"[11] appearance of the great vessels on a short-axis view at the cardiac base. Five had D-transposed great vessels and 4 had L-positioned arteries.

No patient had Doppler evidence of aortic outflow tract obstruction. This fact was verified in 10 of the 14 patients at the time of cardiac catheterization. Pullback left ventricle-to-aorta pressures or simultaneous pressures in the left ventricle and aorta, or both, were not obtained in the remaining 4 patients.

Four children had laminar flow patterns in the pulmonary trunk. Absence of histogram dispersal in these patients indicated unobstructed pulmonary blood flow. Four patients had turbulent systolic flow patterns in the pulmonary artery distal to the valve. Two had smooth patterns proximal to the valve, suggesting that the area of stenosis was localized to the pulmonary valve. The other 2 had turbulent patterns proximal and distal to the valve. In these children, it was difficult to determine whether the obstruction was localized to the infundibular area alone or whether there was additional valvular stenosis.

Four children had absent flow in the infundibular region just proximal to the valve. When the Doppler sample volume was advanced across the valve, a typical Doppler signal of continuous flow was noted, representing either a patent ductus arteriosus or a surgically created shunt (Fig. 8). Each child had a confirmed angiographic diagnosis of pulmonary atresia. The remaining 2 patients had turbulent flow in the pulmonary trunk just distal to the band. The band could be visualized adequately in both cases by 2D echocardiography.

Interatrial septal structure: Subxiphoid 2D-PD was used to view the atrial septum and to evaluate flow patterns. Three patients were believed to have an intact atrial septum. One of these 3 patients had a patent foramen ovale at cardiac catheterization.

Five children had 2D echocardiographic evidence of a dilated patent foramen ovale versus secundum-type atrial septal defect. The ability to distinguish the 2 with confidence was poor. In each patient, a localized gap was noted in the midseptal region. A septum primum flap was not identified in 4 of the 5 patients. In none of these 4 was a distinct septal bulge identified, thereby making the diagnosis of an actual absence of tissue, that is, atrial septal defect, most likely.

In the single patient with redundant primum tissue, there was no septal bulging. Therefore, it was difficult to determine whether there was restriction to flow (as

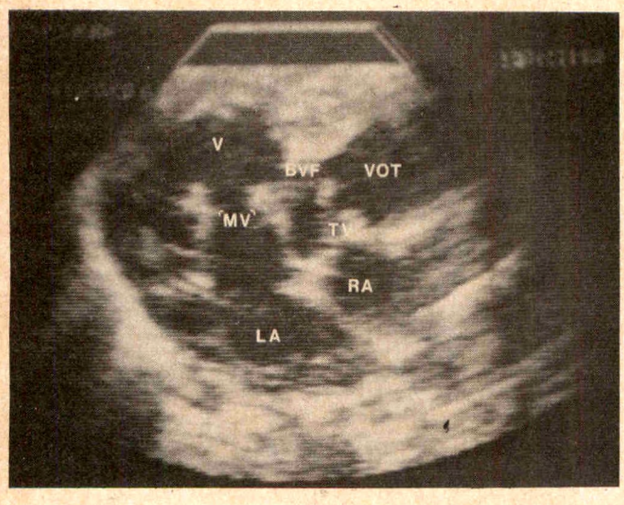

FIGURE 6. A slightly angulated long-axis view in a patient with a single ventricle and 2 AV valves. The tricuspid valve (TV) in this patient was much smaller than the mitral valve (MV). BVF = bulboventricular flange; LA = left atrium; RA = right atrium; V = ventricle; VOT = ventricular outflow tract.

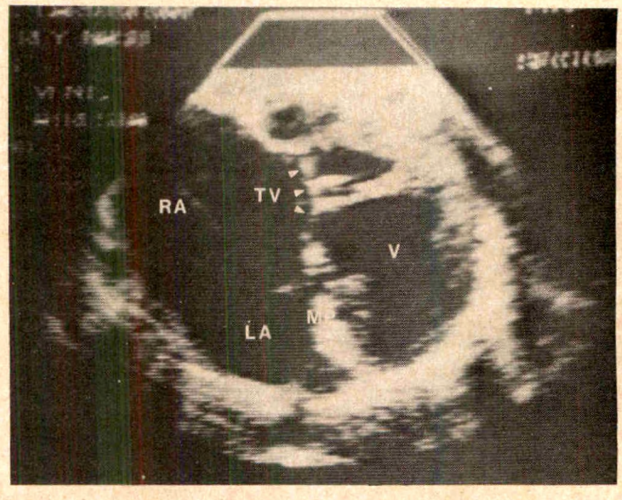

FIGURE 7. Subxiphoid view in a patient with mitral atresia. MP denotes the atretic mitral plate. The **small arrows** indicate the tricuspid valve (TV) anulus. A small remnant of atrial septum divides the 2 atria inferiorly. LA = left atrium; RA = right atrium; V = ventricle.

might be expected with a stretched patent foramen ovale) or a nonrestrictive defect. Four patients had an isolated defect low in the septum, consistent with an ostium primum defect. One patient had multiple (ostium primum and secundum) defects and the remaining patient had total absence of the atrial septum.

Discussion

Two-dimensional–pulsed Doppler echocardiography has greatly enhanced the ability to define the anatomic and hemodynamic characteristics of patients with a univentricular heart. In our 14 patients, an excellent correlation was found between 2D-PD evaluation and angiographic, surgical, and autopsy observations. Our report attempts to noninvasively delineate features of patients with 1 functional ventricular chamber. We hope this concept is useful to the clinician.[22]

Ventricular structure was readily appreciated by the 2D echocardiographic technique. In every patient the outflow chamber, or the absence thereof, was identified. In several patients the trabecular patterns of the ventricles also could be clarified.

Identification of the AV valve orifices also was accurate, which is especially important because angiography may occasionally prove unsuccessful in adequately visualizing these valves. In many cases, this angiographic identification depends on negative contrast effects superimposed on a dye-filled ventricle. This technique may not be very accurate, especially in the presence of small AV valves.

Another problem that may occasionally be masked during catheterization is AV valve regurgitation. Quantification by ventriculography has several inherent problems.[26] Unless proper angiographic angulation is obtained, mild degrees of regurgitation may be missed. By comparison, the Doppler sample volume is readily positioned in the valve orifices to look for mitral or tricuspid regurgitation, or both. This ability to detect AV valve regurgitation may be particularly important in those patients undergoing Fontan-type procedures in which an unrecognized inherently damaged left-sided valve may create significant management problems.[27]

The diagnosis of tricuspid and mitral atresia is readily recognized. "Plate-like" densities can be visualized where normal valves are expected.

As Henry et al[11] aptly noted, the 2D echocardiogram is extremely useful in delineating great vessel relationships. In our patients, the only diagnostic obstacles were in some patients with pulmonary atresia. The short-axis view at the level of the great vessels could readily identify the large aorta; however, it was sometimes more difficult to visualize the atretic pulmonary valve, particularly when the vessels were D-transposed. When the vessels were normally related, there was little difficulty in visualizing the pulmonary trunk distally as it wrapped around the aorta.

The range-gated PD system was particularly useful in evaluating great vessel hemodynamic characteristics. Long- and short-axis, subxiphoid, and suprasternal notch views were used in freeze-frame positioning of the Doppler sample volume. Initial placement was distal to the valve, with continuous recording of the histogram and audio signals as the Doppler sample volume was moved through the valve to a more proximal position in the outflow tract.

In every patient, the Doppler sample volume sweep of the aorta demonstrated laminar or minimally disturbed patterns distal and proximal to the valve. No patient had aortic obstruction on cardiac catheterization, thereby making the ultrasound evaluation sensitive.

Two-dimensional–pulsed Doppler echocardiography was also useful in evaluating the status of the subpulmonary region and pulmonary trunk. Flow patterns were classified by histogram dispersal. Typical high flow patterns, that is, large amplitude spikes with little scatter, were noted in each patient with catheterization-proven unobstructed pulmonary blood flow. Although high flow occasionally resulted in slight broadening of the band pattern, the spectral band in each of these children was more typical of nonturbulent flow (broadband less than 1 cm in amplitude).[28] With these criteria, minimal degrees of valve obstruction may be missed, although these gradients are probably of little clinical significance.

Pulmonary stenosis typically produces a widely dispersed dot pattern during systole, representing turbulence. Initial placement of the Doppler sample volume in the main pulmonary artery accurately demonstrated turbulence in each patient with pulmonary stenosis. In patients with pulmonary arterial bands, the turbulence occurred just distal to the band. As the Doppler sample volume was moved into the outflow tract, the most proximal area of obstruction was identified. When infundibular pulmonary stenosis was present, it was difficult to detect additional valvular stenosis, as turbulence persisted well into the pulmonary trunk.

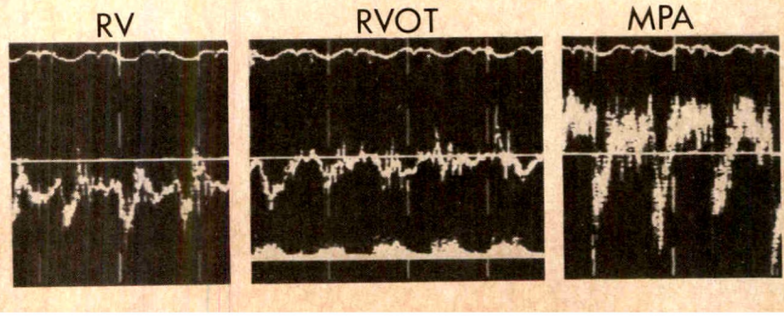

FIGURE 8. Doppler sweep of the right ventricular outflow tract in a patient with single ventricle and pulmonary atresia. A short-axis view was used. The time interval histogram in the body of the right ventricle (RV) illustrates nonturbulent flow directed away from the transducer during systole. When the sample volume is repositioned in the right ventricular outflow tract (RVOT), the amplitude of flow is greatly diminished. Once the sample volume is advanced distal to the atretic pulmonary valve, a widely dispersed dot pattern is demonstrated, associated with a rough continuous audio signal. This pattern is consistent with turbulent flow through a patent ductus arteriosus. MPA = main pulmonary artery.

In the children with pulmonary atresia and ductal- or shunt-dependent pulmonary blood flow, another typical pattern was identified. A continuous flow pattern accompanied by a rough continuous audio signal was typical of the lesion proved by catheterization. This pattern of ductal flow was noted and specific even in patients with high pulmonary blood flow.

Atrial septal morphology was accurately identified in most patients using 2D techniques. In several, however, it was difficult to absolutely distinguish between a secundum type atrial septal defect and a dilated patent foramen ovale. Although each demonstrated a mid-septal gap, absence of a clearly visible septum primum flap (negative echocardiographic finding) was not believed to be synonymous with absence of tissue and, hence, a true atrial septal defect. However, because there was no septal bulging, an atrial septal defect, rather than stretching of a patent foramen ovale, was more likely responsible for the septal dropout. Inability to distinguish the 2 with certainty did not appear clinically significant in patients with a single ventricle and 2 AV valves. In 2 of the 3 patients with mitral or tricuspid atresia, the inability to distinguish the difference has also been clinically unimportant. However, in the remaining patient with tricuspid atresia, the small size of the defect, the presence of primum flap tissue, and the appearance of systemic venous congestion prompted us to recatheterize the patient to be sure the defect was nonrestrictive. The defect proved hemodynamically nonrestrictive.

Although PD evaluation of the atrial septum was carried out in this subgroup of patients, the results were of little value in assisting with clinical management of the patient. The anatomic definition by 2D visualization seemed more important.

The use of 2D-PD has significantly broadened noninvasive expertise. Previously, it was difficult by echocardiography alone to distinguish between patients with single ventricles and those with large ventricular septal defects, complete AV canals, straddling tricuspid valves, and corrected transposition of the great vessels with ventricular septal defects.[3] These conditions can now be readily differentiated and additional information on hemodynamic function can be obtained. Children with semilunar valvular stenosis or AV valve regurgitation or stenosis, or both, can be recognized.

The combination of real-time and 2D imaging with a range-gated PD system represents a very useful tool in pediatric cardiology. This technique provides information that complements the remainder of the noninvasive work-up. The sensitivity and relative specificity of this "duplex" system may provide information that may not be obtainable at cardiac catheterization. Certainly, in the sick newborn in whom invasive procedures carry a high risk, this technique could be used to arrive at a specific diagnosis, so that palliative surgery could be performed. This technique may not totally supplant cardiac catheterization in these complex patients with a univentricular heart; however, angiography may frequently be avoided. Certainly this noninvasive procedure will greatly aid in planning the invasive study and may permit abbreviated studies to be undertaken.

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Prognostic Value of Left Ventricular Size Measured By Echocardiography in Infants With Total Anomalous Pulmonary Venous Drainage

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Left ventricular size may be a determinant of survival in infants with total anomalous pulmonary venous drainage. Right and left ventricular size were measured by M-mode and 2-dimensional (2-D) echocardiography in 13 patients aged 1 day to 4 months (mean weight 4.3 ± 0.42 kg [standard error of the estimate]) who underwent surgery before age 4 months because of severe cyanosis or cardiac failure. Seven patients had venous drainage to a vertical vein, 4 had drainage to the right atrium, and 2 had drainage to the inferior vena cava. Patients were divided into 2 groups: survivors (Group A, n = 8) and nonsurvivors (Group B, n = 5). Death was not statistically related to pulmonary artery pressure, pulmonary venous obstruction, age, or weight at the time of surgery. Right and left ventricular sizes at end-diastole measured from M-mode traces and 2-D echocardiographic 4-chamber views were compared with those from 15 weight-matched control infants. On M-mode and 2-D echocardiography, nonsurvivors had significantly larger right ventricles and smaller left ventricular dimensions than did either control subjects or surviving patients with total anomalous pulmonary venous drainage. The ratio of right to left ventricular size on M-mode and 2-D echocardiography also differed among the 3 infant groups ($p < 0.001$). The ratio of right to left ventricular size differentiated nonsurvivors from survivors and control subjects. Postmortem examinations available in 4 of the 5 nonsurvivors demonstrated that the ratio of right to left ventricular size in the specimens closely agreed with the 2-D echocardiographic ratios. Our study agrees with the impression of other investigators that left ventricular size may be a determinant of survival after repair of total anomalous pulmonary venous drainage.

Total anomalous pulmonary venous drainage (TAPVD) is an uncommon form of congenital cardiac disease in which all pulmonary veins drain to the right atrium, either directly (30%) or through supracardiac (47%) or infracardiac (18%) channels.[1] Clinical manifestations vary but surgical repair is required, with mortality rates ranging from 16 to 30%.[2–6] One factor influencing operative mortality is left ventricular size.[7–9] In 13 patients who underwent early operative repair of TAPVD, we measured right and left ventricular size, as determined by echocardiography, to evaluate its potential use in predicting survival.

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Methods

Patient population: The patient population consisted of 13 infants aged 1 day to 4 months, with a mean weight of 4.3 ± 0.42 kg (standard error of the estimate [SEE]), with a diagnosis of TAPVD confirmed by cardiac catheterization and angiography. Eleven patients were studied at Arizona Health Sciences Center; 2 were studied at Green Lane Hospital, Auckland, New Zealand, during a sabbatical leave of 1 of the authors (DJS). At catheterization, right and left ventricular pressures were measured and their ratios (RV/LV) calculated in 11 of 13 patients; all underwent balloon atrial septostomy during the initial diagnostic study. Oxygen saturation ranged from 51 to 82% and pH was >7.3 in all patients immediately preoperatively. Seven patients had drainage to the superior vena cava through a vertical vein, 4 had drainage to the right atrium, 3 of them to the coronary sinus, and 2 had infradia-

phragmatic drainage with obstruction. All had operative repair before 4 months of age because of cyanosis, unrelenting cardiac failure, severe failure to thrive, or all 3. Patients were divided into 2 groups: Group A, survivors (n = 8); and Group B, nonsurvivors (n = 5). All infants except 2 survivors operated on in New Zealand were operated on by the same surgeon with similar surgical technique, cardioplegic solution, and comparable postoperative care. The cause of death in 1 was uncontrollable hemorrhage, through the anastomosis in a very small left atrium.[10] The other 4 died in a low cardiac output state which could not be reversed either in the operating room or within the first 12 hours postoperatively.

Patients underwent M-mode and 2-dimensional (2-D) echocardiographic examination before surgical repair. Three of 8 survivors were studied serially over a 4 to 6 week period before repair. Fifteen weight-matched normal infants served as the controls.

M-mode studies: M-mode echocardiograms were performed with a Smith Kline Ekoline 20A and a Honeywell 1856 strip chart recorder. Simultaneous lead II electrocardiograms were recorded for timing purposes. Right and left ventricular and left atrial cavity size was measured by the leading edge method according to recommendations of the Committee on M-Mode Standardization of the American Society of Echocardiography[11] with a computerized clinical graphics analyzer (Numonics®).

Two-dimensional studies: Two-dimensional echocardiographic studies were conducted using a 2.4 MHz, electronically focused, phased array device (Toshiba SSH 10A) with a specially damped pediatric transducer (PS 24A-2), a 30° or 82° 5-MHz mechanical sector scanner (Smith Kline Ekosector I) or a prototype 3.5 MHz, dynamically focused, phased array instrument designed and built at the General Electric Research and Development Center, Schenectady, New York.

Studies were recorded on videotapes that were played in slow motion for frame-by-frame analysis. Left and right ventricles were measured from the inner edge of the left or right side of the septum to the inner edge of the corresponding free wall endocardial surface. To maximize ventricular size, measurements were taken at end-diastole at a level just inferior to the atrioventricular valves from an apical 4-chamber plane image[12] (Fig. 1). The left atrium was measured from a parasternal long-axis view at end-systole with the aorta at its most forward point, using the leading edge technique at the level of the aortic valve. The ratio of right to left ventricular size (RV/LV) was calculated from M-mode and 2-D measurements.

Autopsy measurements: Postmortem specimens were available in 4 of 5 nonsurviving infants. The hearts had been fixed in formaldehyde. Right and left ventricular sizes were measured from inner endocardial surfaces using a 4-chamber plane equivalent to the 2-D echocardiographic view. The ratio of right to left ventricular size was calculated from the specimens. Only the ratios were used in data analysis for comparison to echocardiographic dimensions, because the absolute cardiac dimensions had been altered by fixation.

Repeatability of measurements: To determine repeatability, all echocardiographic and postmortem measurements were performed in duplicate, at separate sittings, by 1 inves-

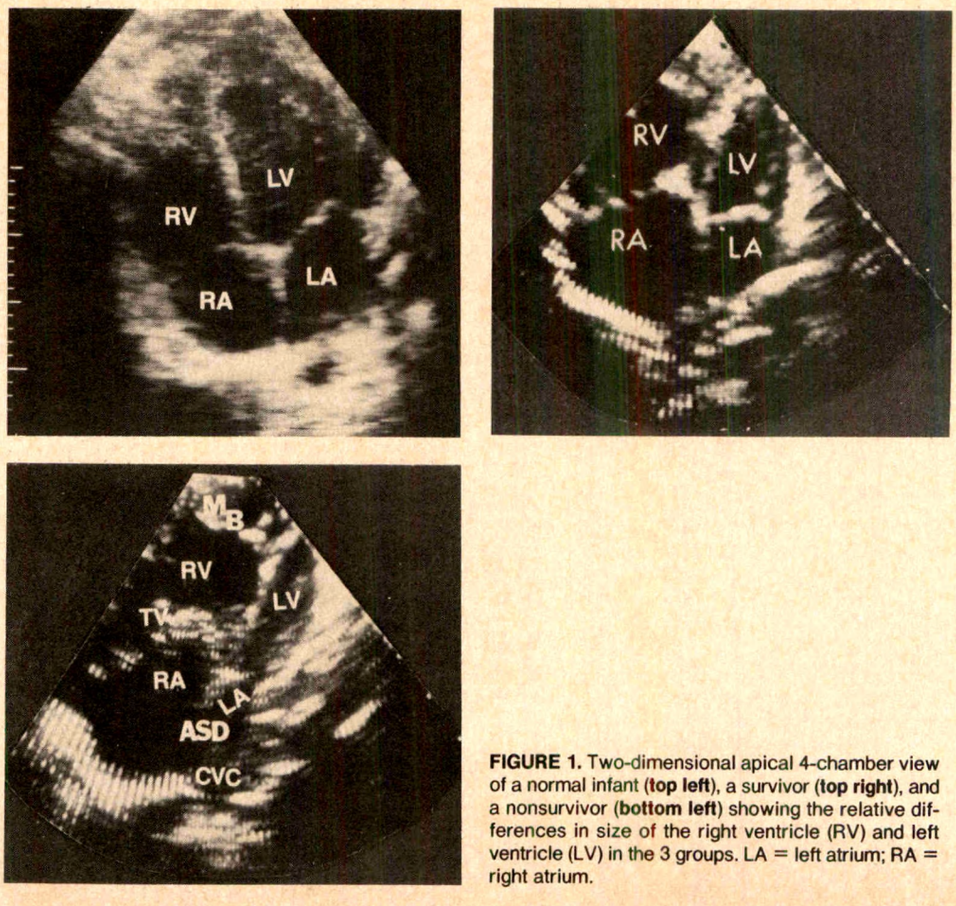

FIGURE 1. Two-dimensional apical 4-chamber view of a normal infant (**top left**), a survivor (**top right**), and a nonsurvivor (**bottom left**) showing the relative differences in size of the right ventricle (RV) and left ventricle (LV) in the 3 groups. LA = left atrium; RA = right atrium.

tigator. To test interobserver variability, all measurements were performed by 2 investigators who were unaware of each other's results, clinical outcome, or patient grouping.

Statistical analysis: Correlation coefficients were calculated to compare M-mode and 2-D results for right and left ventricular and left atrial sizes. Analysis of variance was used to detect differences among the 3 groups (control, survivors, and nonsurvivors) in weight, chamber size, and RV/LV ratios in both M-mode and 2-D views. A restricted least-significant difference comparison was then applied to compare intergroup differences.[13] Student's t test was calculated to compare age at time of surgery, oxygen saturation, and right and left ventricular pressure in surviving and nonsurviving patients. Ratios of RV/LV calculated from 2-D and postmortem data were also compared by the t test. The paired t test was used to analyze measurement repeatability and interobserver variability.

Results

Complete M-mode studies were performed on 10 of 13 infants and complete 2-D echocardiographic examinations were available in 12 of 13 patients. Nonrestrictive interatrial communications were found in all 12 patients on postcatheterization 2-D examination, confirming the adequacy of balloon atrial septostomy in all. Fifteen normal control subjects had acceptable M-mode and 2-D studies.

Clinical and echocardiographic results are summarized in Table I. The 3 groups were comparable with respect to weight. The ratio of right to left ventricular pressure available from catheterization data in 11 of 13 infants <1 month before operation ranged from 0.5 to 1.6 but was not statistically different between survivors and nonsurvivors. Furthermore, age, oxygen saturation, and acid-base balance at operation and sites of drainage of the pulmonary veins were similar in the 2 patient groups. Postmortem examination showed that the ratios of right to left ventricular dimensions in the anatomic specimens closely agreed with ratios derived from the 2-D echocardiographic images (Table I).

M-mode results: Analysis of variance demonstrated that right ventricular and left ventricular sizes were statistically different in the 3 groups ($p < 0.001$ and $p < 0.01$, respectively). Nonsurvivors as a group had smaller left ventricles and larger right ventricles than did either normal subjects or survivors. RV/LV ratios were significantly different in the 3 groups ($p < 0.001$). Control subjects had the smallest mean ratio (mean 0.6 ± 0.15 [standard deviation]), whereas nonsurvivors had the largest (mean 1.4 ± 0.03). All nonsurvivors exceeded a ratio of 1.3. Left atrial size was not statistically different among the 3 groups.

Two-dimensional echocardiographic results (Table I, Fig. 2): Right ventricular dimension was similar in both groups of patients with TAPVD and was larger than that in control subjects ($p < 0.05$). The left ventricle was smaller in nonsurvivors than in either control subjects or surviving infants with TAPVD ($p < 0.05$) (Fig. 1).

The RV/LV ratio best separated the 3 groups ($p < 0.001$): the ratio in control subjects (mean 0.6 ± 0.05) was significantly smaller than that in survivors (Group A) (mean = 1.1 ± 0.13, $p < 0.001$), who in turn had smaller ratios than the nonsurviving infants (mean 1.7 ± 0.29, $p < 0.01$). All nonsurviving infants had absolute ratios >1.4 (Fig. 2). Left atrial size was not significantly different among the 3 groups.

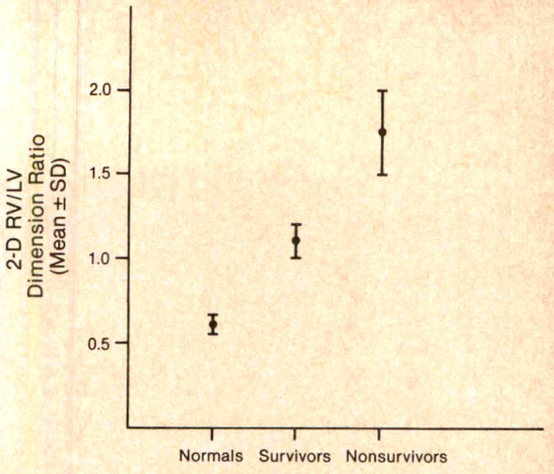

FIGURE 2. Ratio of right ventricular to left ventricular dimension (RV/LV) measured by 2-D echocardiography in normal children and patients with total anomalous pulmonary venous drainage. The RV/LV ratios statistically separated the 3 groups. SD = standard deviation.

Serial 2-D studies: Three patients studied serially belonged to the survivor group. Their RV/LV ratios were all <1.4 and remained so throughout the preoperative course without significant change over 4 to 6 weeks.

Correlation of M-mode and 2-D measurements: Weak but significant correlations existed between M-mode and 2-D measurements of the right ($r = 0.7$, SEE ±0.27, $p < 0.05$) and left ventricle ($r = 0.7 \pm 0.25$, $p < 0.05$). The M-mode echocardiogram usually underestimated ventricular size when compared with the 4-chamber apical plane. A strong correlation was found between M-mode and 2-D echocardiographic measurements of the left atrium ($r = 0.94 \pm 0.1$, $p < 0.001$).

Interobserver variability and errors of repeatability: Cavity measurements derived from M-mode and 2-D images as well as from postmortem specimens were both highly repeatable. The standard error of the mean testing repeatability was <5% when duplicate measurements on a given image or specimen were compared. Interobserver variability in measuring echocardiographic data and autopsy specimens was also <5%.

Discussion

In this study significant right ventricular enlargement and smaller than normal left ventricular cavity dimensions were found in infants with TAPVD. These findings were most pronounced in nonsurviving patients in whom ratios of RV/LV size were statistically higher than those in surviving infants.

Our previous studies[14] and those of others[15] demonstrated that some size differences apparent on the echocardiogram can represent a change in left ventricular shape caused by septal indentation into the left

TABLE I Echocardiographic Data From Patients With Total Anomalous Pulmonary Venous Drainage

Case	Age (days)	O_2 Sat (%)	Wt (kg)	Site	M-Mode Data (cm)				2-D Data (cm)				Pressures (mm Hg)			Angio Obstr	Autopsy Data		
					RV	LV	LA	RV/LV	RV	LV	LA	RV/LV	RV	LV	RV/LV		RV	LV	RV/LV
Group A																			
1	15	74	3.9	SVC	1.4	1.4	1.1	1.0	1.3	1.5	1.1	0.9	70	70	1.0	No	...	...	...
2	60	87	4.8	SVC	2.0	2.0	1.8	1.0	2.6	2.6	1.8	1.0	40	85	0.47	No	...	...	...
3	45	...	4.5	SVC	1.2	1.1	1.2	1.1	1.8	1.7	1.2	1.0	35	85	0.40	No	...	...	...
4	25	87	4.5	SVC	...	...	...	...	1.5	1.2	1.0	1.2	...	...	...	No	...	...	...
5	60	80	4.5	CS	2.0	1.6	1.0	1.2	2.4	2.1	1.1	1.1	70	110	0.63	Yes	...	...	...
6	60	77	4.8	CS	...	...	...	...	1.6	1.6	0.9	1.0	...	...	...	No	...	...	...
7	40	...	3.8	CS	...	...	...	...	1.5	1.2	1.2	1.2	40	80	0.50	No	...	...	...
8	15	79	3.8	RA	1.2	1.0	1.0	1.2	2.0	1.8	0.8	1.1	80	100	0.80	Yes	...	...	...
Group B																			
1	120	78	4.9	CS	2.2	1.6	1.0	1.3	2.2	1.5	1.1	1.4	100	100	1.0	No	2.3	1.5	1.5
2	30	51	4.1	SVC	1.5	1.1	1.1	1.3	1.8	1.2	1.1	1.5	50	95	0.52	No	2.2	1.2	1.8
3	30	83	4.6	SVC	2.0	1.5	1.0	1.3	...	...	...	...	70	115	0.60	No	...	...	...
4	1	65	3.9	INFRA	1.5	1.1	0.8	1.3	1.8	0.9	0.6	2.0	90	85	1.06	Yes	1.8	1.1	1.6
5	2	58	3.8	INFRA	1.7	1.2	0.9	1.4	2.0	1.0	0.6	2.0	110	70	1.57	Yes	1.7	1.1	1.5
Mean A (±SD)	36	80.60 ±5.30	4.32 ±0.42	...	1.56* ±0.40	1.42† ±0.40	1.22 ±0.33	1.10* ±0.11	1.83‡ ±0.46	1.71‡ ±0.46	1.07 ±0.36	1.08* ±0.13	55.8 ±0.19	...	0.62 ±0.25	...	...	...	...
Mean B (±SD)	36	67.0 ±13.0	4.26 ±0.47	...	1.78* ±0.31	1.30† ±0.23	0.96 ±0.11	1.40* ±0.03	1.95‡ ±0.19	1.15‡ ±0.26	0.82 ±0.20	1.74* ±0.29	84.0 ±0.24	...	0.96 ±0.40	...	2.0 ±0.29	1.22 ±0.18	1.6 ±0.14
Normal subjects (±SD)		...	3.57 ±0.76	...	1.05* ±0.21	1.76† ±0.17	1.21 ±0.15	0.60* ±0.15	1.02‡ ±0.12	1.70‡ ±0.21	1.15 ±0.12	0.60* ±.05	...	...	...	...	...	...	...

* Analysis of variance (F ratio) for the 3 groups resulted in $p < 0.001$.
† Analysis of variance resulted in $p < 0.01$.
‡ Analysis of variance resulted in $p < 0.05$.

Age = age at operation; Angio Obstr = evidence of pulmonary venous obstruction by angiography; CS = coronary sinus; INFRA = infradiaphragmatic drainage; LA = left atrial dimensions; LV = left ventricular dimensions; O_2 Sat = arterial oxygen saturation at operation; RA = right atrium; RV = right ventricular dimensions; RV/LV = ratio of right to left ventricular size; SVC = superior vena cava; Site = site of drainage of pulmonary veins; 2-D data = results of 2-D echocardiograms; Wt = weight of patient (kg) at operation.

ventricle as a result of volume and pressure overload of the right ventricle. In this study, cavity measurements were taken only at end-diastole from a 4-chamber apical plane just below the atrioventricular valves in order to maximize chamber dimensions and minimize the possible influence of septal indentation. Agreement between postmortem and echocardiographic RV/LV ratios confirms the relative difference in ventricular dimensions. Subcostal views were not used to measure chamber size because they usually do not permit adequate visualization of the entire right ventricle.

Although M-mode measurements usually underestimated cavity sizes compared with 2-D measurements, RV/LV ratios appeared to cancel the measuring error. The resulting M-mode and 2-D ratios were comparable and equally predictive of survival. All 2-D measurements also tend to underestimate the actual size of imaged structures because of lateral resolution distortion inherent in the method. Nonetheless, using the ratio of the 2-D cavity measurements obtained in the lateral direction from the 4-chamber view negates any differences caused by absolute lateral resolution characteristics of the 2-D echocardiographic systems used in the study, thereby allowing comparison of the data.

Factors influencing mortality in TAPVD are numerous. Although 2 infants with subdiaphragmatic drainage operated on at ages 1 and 2 days both died after surgery, in our group of patients, age at operation,[16–18] oxygen saturation, acid-base balance, site of drainage, or presence of obstruction[16,17] did not specifically differentiate survivors from nonsurvivors. The ratio of RV/LV pressure has been used to suggest the presence of pulmonary venous obstruction and predict survival. Although in our patient group nonsurvivors had higher pressure ratios than did survivors, they were not statistically different, perhaps because of the small number of patients.

Four of the 5 nonsurvivors died in irreversibly low cardiac output. This finding suggests the possibility of inadequate left ventricular size, that is, a left ventricle incapable of sustaining systemic cardiac output in the immediate postoperative period. Similar suggestions have been made in angiographic, surgical, and pathologic studies by others.[7,9,15]

Although cardiac catheterization and selective angiography continue to be crucial in defining hemodynamics and confirming the site of anatomic drainage, serial study of the interrelations between right and left ventricular size in infants with TAPVD is of pertinent clinical interest. Right and left ventricular relations remained stable in our infants studied serially over 4 to 6 weeks; all of these infants survived. Infants with echocardiographic evidence of a rapid increase in right ventricular size or in RV/LV ratio should be considered for prompt operative repair, because these findings imply obstruction to pulmonary venous drainage at either the common pulmonary vein or the atrial septum.

We conclude that serial assessment of chamber size, which can only be performed noninvasively, should be of significant use in studying the course and estimating the prognosis of infants with TAPVD.

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Hypertrophic Obstructive Cardiomyopathy: Ten- to 21-Year Follow-Up After Partial Septal Myectomy

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This study reviews the outcome in 36 consecutive patients who survived partial septal myectomy for hypertrophic obstructive cardiomyopathy operated on between 1960 and 1972. All patients were followed up until death or until June 1981 (mean 13.4 years). Of the 26 survivors, 17 had been more than mildly symptomatic preoperatively, but only 1 remained so postoperatively. The operation was effective in relieving the obstruction (peak systolic pressure gradient reduced from 79 to 8 mm Hg [$p < 0.001$]), and mitral regurgitation was relieved. No survivor's symptoms worsened, but 10 died late—4 suddenly, 5 from congestive heart failure, and 1 from a malignancy. The 10-year survival rate was 77%. No correlation with outcome was found with respect to age, surgical approach, preoperative functional class, pressure gradient, left ventricular end-diastolic pressure, or presence of atrial fibrillation, but atrial fibrillation occurring late postoperatively (12 patients) was associated with an increased frequency of late death (7 of 10 late deaths) or continuing New York Heart Association functional class III status. Early or late postoperative complete heart block occurred in 1 patient each. Thus, these results suggest a favorable effect of operation and support continued surgical intervention for appropriate patients.

The management of patients with hypertrophic obstructive cardiomyopathy has remained a challenge over the past 2 decades since its description in 1957.[1] In the symptomatic patient, efforts have been directed toward relief of symptoms either by beta-adrenergic blocking drugs or by operation (septal myectomy). Propranolol has provided symptomatic relief in 80 to 90% of patients treated at our institution and elsewhere,[2,3] although prevention of sudden death and increase in survival over that of the natural history of the disease remain unproved.[4,5] Recent therapeutic trials with verapamil[6,7] and vigorous antiarrhythmic regimens[8] appear promising.

In patients who do not respond to medical therapy, surgery has played a major role. The techniques of partial septal myotomy and myectomy,[2,9–20] mitral valve replacement,[21,22] construction of a left ventricular outflow tract with a valved conduit,[23] and aortoventriculoplasty[24] have been reported, and their relative merits and disadvantages have been debated.[25,26] Partial septal myectomy has been the surgical procedure of choice at the Mayo Clinic, having been used from 1959 to 1980 in 80 patients with hypertrophic obstructive cardiomyopathy. This report presents extended long-term follow-up of the operative survivors of the first 40 patients (1959 through 1972) with specific emphasis on the late postoperative clinical course, complications, and modes of death. The initial Mayo Clinic experience with surgical treatment[20,27] and early surgical follow-up of this same group of patients were reported previously.[28]

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Methods

In the early surgical follow-up of this group of 40 patients, there were 4 operative deaths (death during operative hospitalization or within 30 days of operation), for an operative mortality of 10%, the details of which were previously reported.[28] The patients constituting the present study group are the 36 surgical survivors, who were followed up to June 1981 or until death. No patients was lost to follow-up, the duration of which ranged from 2 to 21 years (mean 13). Follow-up information was obtained for all patients from examinations at the Mayo Clinic or from physician telephone interviews and correspondence with the patients, relatives, and referring physicians.

The study group of 36 included 28 adults and 8 children (22 male and 14 female). The mean age at operation was 31 years (range 16 months to 63 years). All patients had clinical and hemodynamic documentation of hypertrophic obstructive

TABLE I Symptoms Preoperatively and at Long-Term Follow-Up in 36 Patients

	Preoperatively		Postoperatively	
Symptom	n	%	n	%
Dyspnea	27	75	18	50
Angina	24	67	12	33
Near-syncope	11	31	5	14
Syncope	8	22	3	8

cardiomyopathy.[28] Only 7 patients took propranolol preoperatively.

This group of patients was highly symptomatic, the most common preoperative symptoms being dyspnea and angina (Table I). Eleven patients (31%) had angina, dyspnea, and syncope or near-syncope. The New York Heart Association functional classification was as follows: 26 class III (symptoms with ordinary sedentary activity), 7 class II (symptoms with strenuous exertion), and 3 class I (asymptomatic). The 3 asymptomatic patients were children (aged 16 months and 11 and 14 years) with severe left ventricular outflow tract obstruction (gradients of 107 to 160 mm Hg).

The mean basal* left ventricular outflow peak systolic pressure gradient was 79 mm Hg (range 6 to 160): 22 patients had basal gradients of ≥70 mm Hg and 7 had gradients ≤40 mm Hg. Four of the 7 patients with low basal left ventricular outflow gradients were stimulated to gradients of 57, 92, 96, and 130 mm Hg, respectively, after the administration of isoproterenol. The left ventricular end-diastolic pressure averaged 20 mm Hg (range 7 to 37) and was normal (≤14 mm Hg) in 7 patients. Twenty-eight patients (78%) had mitral regurgitation on left ventriculography (mild 15, moderate 11, and severe 2).

The surgical approaches for septal myectomy in the 36 survivors were as follows: transaortic in 19, transventricular in 13, and combined transaortic and transventricular in 4. Since 1968, the transaortic approach alone was used. A wide and long resection of the hypertrophied muscle from the left ventricular outflow tract was accomplished with the use of cardiopulmonary bypass. One 37-year-old man required mitral valve replacement in addition because of a large perforation of the anterior leaflet of the mitral valve from infective endocarditis.

With respect to statistical methods, 1-sided sign tests were used for comparisons of preoperative versus postoperative clinical variables. The survival curve was computed by means of the Kaplan-Meier (actuarial) method.[29] To determine whether a given variable was associated with survival (for example, whether male subjects survived significantly better than female), we performed 2-sided tests.[30] Log-rank tests were used for variables that were dichotomous (such as sex); 2-sided logit-rank tests[31] were used for variables that were continuous (such as age).

Results

Symptoms at long-term follow-up: All symptoms occurred less often postoperatively than preoperatively (Table I). The most dramatically relieved symptom was angina pectoris, which decreased in frequency from 67 to 33%. Seven of 8 patients with frank syncope preoperatively had no recurrence at long-term follow-up, although an additional 2 patients had new episodes of syncope postoperatively. The disabling triad of angina, dyspnea, and syncope or near-syncope occurred in 11 patients (31%) preoperatively and in only 2 patients (6%) postoperatively ($p < 0.011$).

Electrocardiographic abnormalities: The most common arrhythmia documented at long-term follow-up was atrial fibrillation, which occurred in 12 patients (33%); it was paroxysmal in 4 and sustained in 8. Two of these patients were the only 2 who had atrial fibrillation preoperatively. One patient with chronic atrial fibrillation is in functional class III, and 7 patients with postoperative atrial fibrillation are dead. However, atrial fibrillation was not invariably associated with clinical deterioration. Four patients with atrial fibrillation, known to be present for 2 to 13 years, are in class I or II; 1 of them has required implantation of a permanent pacemaker for slow ventricular rate. One systemic and 2 pulmonary embolic events occurred in patients with atrial fibrillation, none of whom were taking anticoagulant medication. No embolic event occurred in patients who were not in atrial fibrillation.

Complete heart block was present in 2 patients, 1 as an operative complication and the other as an acquired condition 4 years postoperatively in a setting of right bundle branch block and left axis deviation. Both of these patients are being controlled with permanent implanted ventricular demand pacemakers and are in class I and II, respectively. The most common new postoperative conduction abnormality was left bundle branch block in 15 of 36 patients (42%). Intraventricular conduction delay occurred in 7 of 36 (19%) and new right bundle branch block occurred in 4 of 36 (11%) patients. The presence of postoperative left bundle branch block was analyzed as a discrete variable and it was found not to be predictive of death versus survivorship.

The data were analyzed to determine whether electrocardiographic voltage of left ventricular hypertrophy regressed postoperatively with relief of outflow obstruction. This question remains unanswered because conduction defects were a common finding after surgery and made pre- and postoperative electrocardiographic comparisons difficult. Hence, such a comparison was feasible in only 10 patients who had evidence of left ventricular hypertrophy on the preoperative electrocardiogram. Their postoperative electrocardiogram demonstrated left ventricular hypertrophy unchanged in 4, present with decreased voltage in 2, and absent in 4. Postoperative conduction defects and axis shifts also made comparisons of pathologic Q waves difficult. These were present on electrocardiograms in 13 of 36 patients (36%) preoperatively. Pathologic Q waves disappeared after myectomy in 10 of 13 patients and new pathologic Q waves appeared postoperatively in 3 patients.

Postoperative cardiac catheterization data: Cardiac catheterization was performed in 22 patients at a mean interval of 7 years after operation. The decision to perform catheterization was made clinically on an individual basis by the patients' physician. Although these 22 patients are a select subgroup and may not

* The term *basal* refers to the resting state, not influenced by drug or exercise intervention.

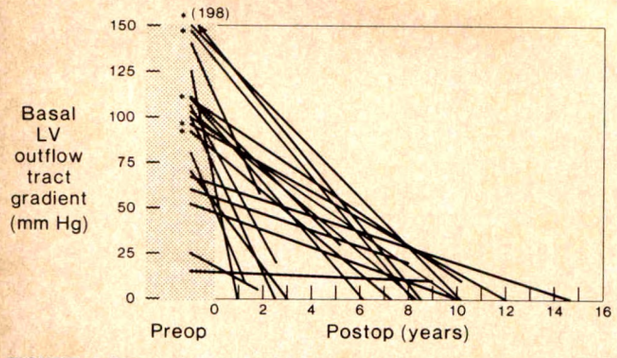


FIGURE 1. Comparison of basal left ventricular (LV) outflow gradient pre- and postoperatively. Data were obtained in 20 patients. **Asterisks** = provoked.

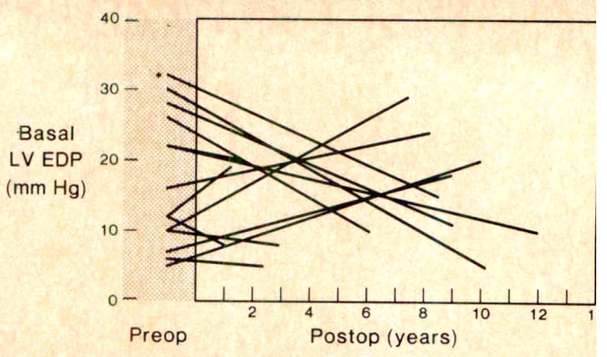


FIGURE 2. Comparison of basal left ventricular end-diastolic pressure (LV EDP) pre- and postoperatively. Data were obtained in 15 patients. **Asterisk** = provoked.

reflect the experience of all 36 patients, some trends are apparent. Figure 1 displays postoperative basal peak gradients across the left ventricular outflow tract compared with the preoperative basal values. A decrease was observed in all 22 patients. The mean postoperative gradient was 8 mm Hg compared with 79 mm Hg preoperatively ($p < 0.001$). All had postoperative gradients ≤20 mm Hg, except for 1 patient with a gradient of 58 mm Hg (preoperative gradient 140 mm Hg). Left ventricular end-diastolic pressures showed no significant change from the preoperative values (Fig. 2), decreases being observed in 8 of 14 patients. Left ventricular end-diastolic pressure was normal after myectomy in 7 of the patients who were catheterized, and all of these patients were alive in functional class I or II at follow-up.

Mitral regurgitation was found in 28 of 36 patients (78%) preoperatively and in only 6 patients postoperatively. However, because the entire study group has not had postoperative left ventriculography, the precise incidence of postoperative mitral regurgitation is unknown. In the patients who had left ventriculographic data available both pre- and postoperatively, mitral regurgitation was present in 13 before myectomy and in 5 postoperatively. In none of these comparison patients was the degree of mitral regurgitation worse after myectomy, and in no patient did it appear when there was none preoperatively.

The new finding of mild aortic regurgitation was documented at catheterization in 2 patients and on clinical examination in 2 patients. Of interest, all 4 had undergone myectomy through the aortic approach. In contrast, no aortic regurgitation was found in patients in whom the transventricular or combined approach had been used. Tricuspid regurgitation was reported in 2 patients and a small ventricular septal defect (Q_p/Q_s 1.4) in 1. Coronary angiography was performed in only 3 patients with angina preoperatively. Information on coronary anatomy was present in 7 patients at follow-up: 6 by angiography and 1 by autopsy. Of the 3 patients with preoperative angiograms, 2 had postoperative studies. One had significant progression of the disease over a period of 7 years (minor disease of the circumflex artery preoperatively to totally occluded left anterior descending artery and 70% obstruction of the right coronary artery), and the other had normal coronary arteries pre- and postoperatively. Three patients had high-grade obstructive coronary artery disease in 2 or 3 major vessels; 4 patients had minimal or no coronary artery disease. The 2 patients with 3-vessel disease and 1 with no significant disease are in the death group.

The data were analyzed in an attempt to find preoperative hemodynamic predictors for death versus postoperative survivorship. There was no statistically significant association between survival and preoperative basal left ventricular outflow gradient or left ventricular end-diastolic pressure.

Postoperative echocardiography: M-mode echocardiographic data were available in 25 patients at a mean of 10 years postoperatively. The most notable finding was a normal left ventricular cavity size (left ventricular internal dimension in diastole, ≤56 mm) and normal function in all 25. The left atrial size was normal (19 to 40 mm) in 12 and enlarged (43 to 52 mm) in 13. Mild systolic anterior motion of the mitral valve was present in 11 patients; cardiac catheterization data, which were available in 6 of these 11 patients, showed no significant residual basal gradient (0 to 20 mm Hg).

Deaths: Ten late deaths occurred (after a mean of 13.4 years of follow-up), leaving 26 long-term survivors.

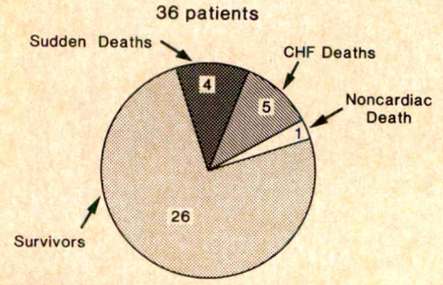


FIGURE 3. Mortality (cardiac and noncardiac) and survivorship in 36 patients surviving septal myectomy. Follow-up is 7 to 19 years (mean 11.7). CHF = congestive heart failure.

TABLE II Sudden Death Group (4 Patients)

Age at Death (yr)	Sex	Postoperative Survival (yr)	Electrocardiogram at Last Follow-Up	NYHA Class (I to IV) (Preoperative/Postoperative)	Drug Therapy Preceding Death
14	F	1.8	WPW	II/II	Digoxin
21	M	1.7	LBBB, LAD	II/II	Propranolol
27	M	10	LBBB, AF	III/I	None
47	F	3.7	LBBB, AF	III/I	None

AF = atrial fibrillation; LAD = left axis deviation; LBBB = left bundle branch block; WPW = Wolff-Parkinson-White syndrome.

TABLE III Intractable Congestive Heart Failure Group (5 Patients)

Age at Death (yr)	Sex	Postoperative Survival (yr)	Electrocardiographic Findings at Last Follow-Up	Associated Conditions	Drug Therapy Preceding Death
40	F	17.1	AF, LAD, IVCD	Pulmonary embolism	Digoxin, propranolol, quinidine, anticoagulant
47	F	10.4	RBBB, LAD, AF	Myocardial infarction	Digoxin, diuretic, procainamide, anticoagulant
48	M	11.5	LBBB, LAD, AF	ASHD	Digoxin, diuretic
55	F	8.0	LAD, anterior infarct pattern, AF	COPD	Digoxin, propranolol, diuretic, anticoagulant
57	M	8.7	LBBB, AF	ASHD, bowel infarction	Isosorbide dinitrate

AF = atrial fibrillation; LAD = left axis deviation; LBBB = left bundle branch block; WPW = Wolff-Parkinson-White syndrome.

Four deaths were sudden, 5 were from congestive heart failure, and 1 was from a noncardiac cause (metastatic breast cancer) (Fig. 3).

The deaths were analyzed from the standpoint of several discrete and continuous variables to find predictors of death versus survivorship. Of the 9 cardiac deaths, 4 occurred in the group in which myectomy was performed from the transaortic approach (4 of 19, or 21%) and 5 in those with the ventricular or combined approach (5 of 17, or 29%). This apparently higher incidence of death in patients undergoing myectomy from the transventricular or combined approach did not achieve statistical significance. Furthermore, the 2 groups are not directly comparable because of differences in duration of follow-up. These differences are due to the fact that the transventricular approach was the earlier approach to myectomy at this institution. Other variables, including age at operation, preoperative functional class, and the presence of preoperative congestive heart failure or atrial fibrillation, were analyzed. No statistically significant associations with survivorship were found.

Table II gives details of the 4 patients who experienced sudden death. Sudden death occurred an average of 4.3 years postoperatively. The 4 were asymptomatic or mildly symptomatic and were engaged in sedentary activity at the time of death. Because of the early nature of the study, only 1 of these patients was taking propranolol (120 mg/day) at the time of death.

Late deaths (Table III) from intractable congestive heart failure occurred late postoperatively, at a mean of 11 years. All of these patients were in atrial fibrillation for 6 to 108 months before death. After initial clinical improvement in 2, all had deteriorated to class IV status preterminally. Documented severe 3-vessel coronary artery disease was present in 2. One patient had autopsy evidence of left ventricular cavity dilatation in the presence of massive free wall and septal hypertrophy and severe coronary artery disease. Other serious complicating conditions included pulmonary embolism (1 patient), bowel infarction due to mesenteric artery thrombosis (1), and chronic obstructive pulmonary disease (1).

Postoperatively, the patients who died were characterized by a higher incidence of atrial fibrillation at the time of death (7 of 9, or 78%) compared with the long-term survivors at the time of follow-up (6 of 26, or 23%). Congestive heart failure and the concomitant disease were also more prevalent in the group who died.

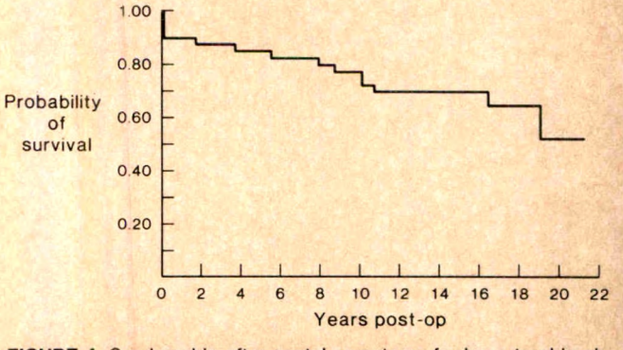
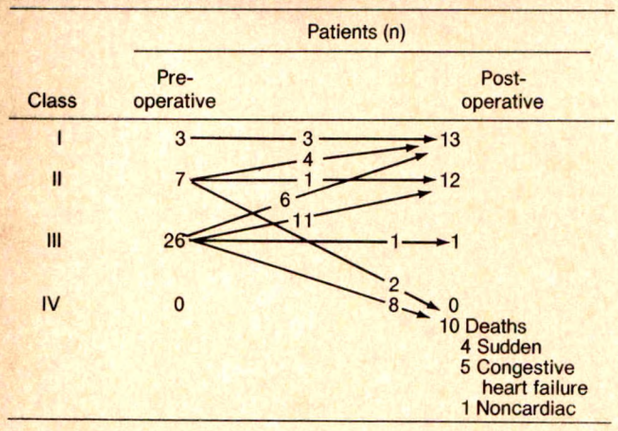


FIGURE 4. Survivorship after septal myectomy for hypertrophic obstructive cardiomyopathy, including operative mortality and postoperative deaths (excluding 1 noncardiac death).

TABLE IV Functional Class in 36 Patients



Survivorship and functional status at long-term follow-up: The survival curve of the group, including 26 survivors, 4 operative deaths, and 9 cardiac deaths (excluding 1 noncardiac death), is depicted in Figure 4. The 10-year survival rate was 77.5%, including 4 operative deaths, or 86.1% when these deaths are excluded.

Also of importance is the question of whether symptomatic improvement occurs after operation and whether it is maintained over an extended follow-up period. Table IV shows the current functional status of the study group. Twenty-five survivors are either asymptomatic or mildly symptomatic. Only 1 is limited to class III status. The improvement in functional class in 3 patients was probably related to the addition of propranolol in 2 patients and the discontinuance of smoking in 1 patient whose primary symptom was dyspnea.

Overall, 21 of 26 (81%) of the long-term survivors perceived themselves as being symptomatically improved by at least 1 functional class over their preoperative status; of the remaining 5 patients, 3 continued to be asymptomatic and 2 remained in their preoperative functional class. Of note, the 3 patients who remained asymptomatic are the 3 pediatric patients with severe left ventricular outflow tract obstruction who were operated on in the hope of preventing early mortality. They have now been followed up 8.8, 13.8, and 17.0 years.

Most of the survivors are pursuing normal activities. These include the roles of active housewife (with successful pregnancies), businessman, farmer, plumber, physician, lawyer, policeman, student, and active retired person. The 2 oldest survivors are 76 and 77 years old, have been followed up 12.6 and 15.3 years, and are both in functional class II.

Discussion

This is the longest survivorship study published and represents 100% follow-up of patients in whom hypertrophic obstructive cardiomyopathy was managed by partial septal myectomy. It provides a retrospective look at 495 patient-years of follow-up in terms of significant cardiac events. Of the long-term survivors, 92% remain symptomatically improved or asymptomatic, and the symptom most frequently relieved was angina pectoris. After a mean follow-up of 13.4 years, 72% who survived operation are alive; 16 of the 36 survivors have been followed up >15 years. The overall 10-year survivorship rate, including operative mortality, was 77% (2.6% mortality per year). The postoperative (excluding operative mortality) 10-year survivorship rate was 86% (1.6% mortality per year), which parallels the National Heart, Lung, and Blood Institute's surgical experience.[14] This compares favorably with the 4% mortality per year cited in the natural history study of propranolol-treated and untreated patients with hypertrophic obstructive cardiomyopathy.[4] However, the implication that operation may increase long-term survivorship is made with caution because surgical and nonsurgical groups have not been randomized and may not be comparable. Furthermore, in this retrospective study, the influence of postoperative medical management on survivorship cannot be assessed.

The contention has been forwarded by Oakley[32] that the long-term outcome of septal myectomy is deleterious and that the left ventricular outflow gradient is abolished because of reduction in ventricular performance from myocardial damage. Although the present retrospective study lacks objective measurement of left ventricular function in all patients postoperatively, the extended long-term survivorship and favorable clinical status of these long-term survivors militate against the likelihood of significant impairment of global left ventricular function. In the patients in whom invasive and noninvasive studies are available postoperatively, we have not observed a significant increase in left ventricular end-diastolic pressure to suggest decreased ventricular compliance or left ventricular cavity dilatation on echocardiography or ventriculography to suggest myocardial damage and failure except in 1 patient with severe concomitant coronary artery disease. Our impression of adequate left ventricular performance after septal myectomy is supported by treadmill exercise studies by Redwood et al,[33] who demonstrated increased exercise performance in 89% of their study group (25 of 28 patients). In addition, radionuclide studies by Borer et al[34] showed normal or supernormal resting ejection fractions in 90% of their postmyectomy patients (19 of 21 patients).

Sudden death remains the most challenging aspect of the disease. Not only may it be the first definitive manifestation of hypertrophic cardiomyopathy,[35] but also good clinical predictors of its occurrence are lacking. In the present operative series, sudden death occurred late postoperatively in 11%. These patients were relatively young (mean age 33 years) and were doing well clinically at the time of death. The incidence of sudden death suggests that the myopathic ventricle continues to be arrhythmogenic, an aspect of the disease that operation does not appear to eliminate. Of interest, however, the presently reported sudden death rate of 11% (in surgically treated patients over an average follow-up of 13.4 years) is lower than the 18% incidence of sudden death (in a group of 101 patients treated medi-

cally over 4.7 years of follow-up) reported by Shah et al[4] and the 40% incidence of sudden death (in a group of 20 children treated medically over an average follow-up period of 7.4 years) reported by Maron et al.[36] Clinical studies by Fiddler et al[37] and McKenna et al[5] indicate that the incidence of sudden death is higher in the pediatric age group. Although the lower incidence of sudden death in the present series (which includes 9 patients 17 years of age or younger) is encouraging, the role of myectomy in preventing sudden death in young patients with hypertrophic obstructive cardiomyopathy remains to be determined.

Late postoperative death from congestive heart failure occurred in 14% of the study group at a mean of 11.1 years postoperatively. These patients were older compared with those in the sudden death group (age 40 to 57 years, mean 49), and all were in atrial fibrillation. These patients had serious concomitant diseases (coronary atherosclerosis, pulmonary embolism, chronic obstructive pulmonary disease, and bowel infarction), which were undoubtedly related to the presence of congestive heart failure and probably related to their deaths.

The present study shows, as has previously been thought, that partial septal myectomy does not prevent sudden and late cardiac death. Furthermore, preoperative predictors of postoperative death have not been found. In the present study, none of the following indexes predicted death versus survivorship: age at operation, preoperative functional class, left ventricular outflow tract gradient, left ventricular end-diastolic pressure, presence of preoperative congestive heart failure or atrial fibrillation, surgical approach, or postoperative left bundle branch block. The reason may be that, from a statistical standpoint, the number of patients in this study group is small. However, Maron et al[14] also found that surviving patients and those who died late of hypertrophic cardiomyopathy did not differ with respect to preoperative symptoms, left ventricular outflow gradient, left ventricular end-diastolic pressure, postoperative functional class, or electrocardiographic abnormalities. In the absence of preoperative predictors of operative success, timing and selection for operation are primarly dictated by the need to relieve the patient's symptoms and disability.

The surgical mortality for septal myectomy for hypertropic obstructive cardiomyopathy has declined from 10% in the first 40 patients (1959 to 1972) to 5% in the succeeding 40 patients (1973 to 1980) who were operated on at the Mayo Clinic. This is a gratifying although not a statistically significant improvement. Because of the acceptably low operative mortality and the comparatively favorable late survival and symptomatic status, we continue to believe that partial septal myectomy is indicated in the symptomatic patient with left ventricular outflow tract obstruction who is not responsive to adequate medical treatment (beta-adrenergic blocking agents, verapamil, and antiarrhythmic drugs). Although this point is controversial, the favorable outcome thus far for our 3 asymptomatic children with left ventricular outflow gradients of more than 100 mm Hg, as compared with reported results for medical management of such patients, strengthens our belief that the asymptomatic patient with severe ventricular outflow obstruction in the basal state should receive surgical consideration, especially when the patient is young.

These recommendations are made in the belief that intraventricular obstruction is an important element of this disease and that it can be alleviated, with the expectation of improved long-term survival and relief of symptoms. However, the cardiomyopathic process remains a major factor that affects the patient's ultimate course.

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Clinical and Morphologic Cardiac Findings After Anthracycline Chemotherapy

Analysis of 64 Patients Studied at Necropsy

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The relation between clinical evidence of and histologic signs of anthracycline cardiotoxicity was evaluated by reviewing the clinical and morphologic findings in 64 patients studied at necropsy, all of whom had received doxorubicin or daunorubicin chemotherapy during life. Of the 64 patients, 20 (31%) had documented clinical toxicity consisting of impaired left ventricular systolic performance; in 7 (35%) of these 20 patients, histologic signs of toxicity were absent. In the remaining 13 patients with clinical toxicity, histologic signs of toxicity ranged from mild to severe. Of the 44 (69%) patients without clinical signs of drug toxicity, 21 (48%) had no histologic sign of cardiotoxicity; in 23 (52%) of the patients without clinical toxicity, however, morphologic signs of cardiotoxicity were nevertheless present—mild in most patients, but extensive in 4. Signs of extensive histologic toxicity (19 [30%] of 64 patients) were associated with large doses (>450 mg/m^2) of the drug, mediastinal irradiation, and age >70 years. This study suggests that attempts to monitor cardiotoxicity by serial evaluation of cardiac histology in patients undergoing anthracycline chemotherapy may be seriously limited by the fact that clinical evidence of toxicity may be present without histologic signs of toxicity; likewise, histologic signs of anthracycline toxicity may be present without clinical evidence of toxicity.

The anthracycline drugs doxorubicin (Adriamycin™) and daunorubicin (Daunomycin™) are 2 of the most effective chemotherapeutic agents presently available for treatment of patients with solid tumors and leukemias.[1] Cardiac toxicity is a well-recognized complication of these agents and is frequently the dose-limiting factor in their administration.[2,3] Although endomyocardial biopsy has been used in several centers to monitor patients receiving anthracycline chemotherapy,[4] limited information is available regarding the results of necropsy examination of patients who have received these drugs.[5–7] The present study was designed to determine (1) the extent of morphologic cardiotoxicity at necropsy in patients treated with anthracycline compounds, and (2) the degree to which the results of morphologic examination of necropsy hearts correlated with clinical evidence of cardiac dysfunction.

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Methods

Review of the clinical records of all patients with malignant neoplasms who died and underwent necropsy examination at the National Cancer Institute, Bethesda, Maryland, between January 1, 1970, and June 30, 1979, revealed 93 patients who had been treated with anthracyclines. In 11 patients, the gross and/or histologic material available for review was inadequate; in 18 additional patients, interpretation of both clinical and morphologic cardiac findings was complicated by medical problems such as severe anemia, renal failure, hemosiderosis, and myxedema. These 29 patients, therefore, were eliminated from further study. The remaining 64 patients form the basis of the present study. Review of gross and histologic findings and reexamination of the hearts from these 64 patients were performed without knowledge of the clinical cardiac findings.

The hearts of all 64 patients were evaluated grossly for pericardial disease, chamber dilatation, mural thrombus, and foci of fibrosis or necrosis. Histologic sections from the left ventricular free wall, ventricular septum, and right ventricular free wall were stained with hematoxylin-eosin and phosphotungstic acid hematoxylin. Each section was examined by 3 observers, who, by consensus, assigned to it a histologic score. Two characteristics were used to score the extent of histologic cardiotoxicity: vacuolization of cardiac muscle cells (Fig. 1a)

TABLE I Clinical and Morphologic Findings in 20 Patients With Clinical Evidence of Anthracycline Toxicity

Age (yr) & Sex	Interval Onset Sx to Death	Physical Examination			CXR		Echo		Hemodynamic Data		Cardiac Therapy		
		JVD	Rales	S_3	CE	PVH	LVd	FS	CVP	PAOP	Dig	Diur	Improved
Patients Without Histologic Signs of Anthracycline Toxicity													
5F	18 d	0	+	+	0	+	–	–	–	–	+	+	+
15M	1 d	+	+	+	+	+	50	0.16	20	–	+	+	0
18M	7 d	+	+	+	+	+	–	–	20	–	+	+	0
26F	1 d	0	+	+	0	+	–	–	18	–	+	+	0
37F	2 mo	+	+	+	+	+	–	–*	–	–	+	+	+
61M	7 mo	0	0	+	+	+	–	–	–	–	+	+	+
61M	14 mo	+	+	0	+	+	65	0.28	15	–	+	+	+
Patients with Histologic Signs of Anthracycline Toxicity													
13M	6 d	+	0	+	+	+	47	0.16	–	–	+	+	0
39M	4 mo	0	+	+	+	+	51	0.18	9	18	+	+	+
21M	15 d	+	+	+	+	0	58	0.19	20	20	+	0	0
22F	5 wk	0	+	0	+	0	52	0.19	18	–	+	+	+
35F	11 mo	+	+	+	+	+	54	0.19	–	22	+	+	+
78M	2 d	+	+	+	+	+	–	–	–	–	+	+	0
12M	9 d	+	+	0	+	+	46	0.30	17	–	+	+	+
15F	3 mo	0	0	+	+	0	61	0.10	–	18	+	+	+
29F	7 d	+	+	+	+	+	55	0.27	16	20	+	+	0
49F	1 mo	0	0	0	+	0	52	0.08	–	26	+	+	0
5M	17 d	+	0	+	0	0	–	–	–	–	+	+	+
33F	2 mo	+	0	+	0	0	44	0.23	–	–	+	+	+
11F	4 wk	+	+	+	+	+	46	0.13	–	–	+	+	+

* Preejection period/left ventricular ejection time = 0.61.

CE = cardiac enlargement; CVP = central venous pressure; DA = daunorubicin; DO = doxorubicin; DIG = digitalis; Diur = diuretic; FS = fractional shortening; Histo Tox = histologic toxicity; JVD = jugular venous distention; LVd = left ventricular end-diastolic dimension; Med Irrad = mediastinal

and myofibrillar dropout (Fig. 1b). The severity of each of these 2 histologic features was assessed for each section of the myocardium according to the following scale: 0 = none, 1 = mild, 2 = moderate, and 3 = extensive. The final score of histologic cardiotoxicity for a particular patient was arrived at by adding the highest grade for vacuolization and the highest grade for myofibrillar dropout observed on any of the various sections of myocardium from the patient. For example, a patient who received a score of 2+ for vacuolization and 1+ for myofibrillar dropout would receive a final score of 3+ for histologic cardiotoxicity.

The hospital records of all 64 patients were reviewed without knowledge of the necropsy findings. Echocardiograms performed in 26 patients also were reevaluated without knowledge of necropsy findings or of the original interpretation of the study.

Statistical significance regarding characteristics of groups with and without clinical or histologic toxicity was assessed by the chi-square test.

Results

Patients with clinical evidence of drug toxicity: Of the 64 patients, 20 (31%) had clinical evidence of cardiotoxicity (Table I). These 20 patients included 10 males and 10 females, aged 5–78 years (average 29). Their total dose of anthracycline drug ranged from 85 to 900 mg/m^2 (average 450), administered over a period of 4 to 156 weeks (average 41). Four patients also received mediastinal irradiation to a total dose of 4,000, 9,450, 12,450, and 12,600 rads, respectively. In 16 of these 20 patients, evidence of cardiotoxicity included hemodynamic documentation (12 patients) (elevated central venous pressure or elevated pulmonary capillary wedge pressure, or both) and/or echocardiographic documentation of decreased fractional shortening (11 patients); in the remaining 4 patients, the diagnosis of a drug-induced cardiomyopathy was based on a combination of physical signs of cardiac decompensation (jugular venous distention, inspiratory rales, S_3 gallop sound) and radiographic signs of pulmonary venous hypertension and cardiomegaly. All 20 patients with clinical signs of drug toxicity received digoxin and 10 also received diuretics.

In 7 of the 20 patients with clinical signs of drug toxicity, the pericardial sac contained >50 ml of fluid (average 186, range 80 to 300). Two of these 7 patients had received mediastinal irradiation, and in 1 the pericardial fluid was grossly hemorrhagic; in the remaining 6 the fluid was serosanguinous. None of the 7 patients had cardiac metastases. The average heart weight in the 17 adult patients with clinical signs of drug toxicity was 358 g (range 240 to 500) (Table I). In 18 of the 20 patients, the heart weight observed exceeded that predicted according to body weight[8] by an average of 106 g. In 11 of the 20 patients, both ventricular cavities were dilated, while in 4 other patients the left ventricle alone was dilated; in the remaining 5 patients, neither ventricular cavity was dilated. The presence or absence of cavity dilatation at necropsy was *not* a function of the interval between the onset of clinical signs of toxicity and death. In 2 patients, the dilated ventricular cavities contained mural thrombus (Fig. 2); neither patient had a history of peripheral embolic events.

Histologic signs of cardiotoxicity were observed in 13 of the 20 patients with clinical signs of drug toxicity (Tables I and II): these 13 patients included 10 of the 15 patients with and 3 of the 5 without cavity dilatation. The combined histologic scores for toxicity among these 13 patients ranged from 1 to 5 (average 2.3).

TABLE I (Continued)

Age (yr) & Sex	Oncologic Therapy: Total Anthracycline (mg/m²)	Oncologic Therapy: Duration Rx (wks)	Oncologic Therapy: Total Rads Med Irrad	Gross Findings: Heart Wt (g) Obs (Pred)	Gross Findings: Dilated Ventricles	Histologic Findings: Myocyte Vacuoles	Histologic Findings: Myofibrillar Dropout	Histologic Findings: Histo Tox score
Patients Without Histologic Signs of Anthracycline Toxicity								
5F	345(DA)	26	0	150(99)	+	0	0	0
15M	530(DA)	32	0	450(253)	+	0	0	0
18M	630(DA)	32	0	295(297)	0	0	0	0
26F	330(DA)	12	0	320(258)	+	0	0	0
37F	550(DO)	88	0	270(260)	+	0	0	0
61M	210(DO)	4	0	396(350)	0	0	0	0
61M	250(DO)	8	0	500(352)	+	0	0	0
Patients With Histologic Signs of Anthracycline Toxicity								
13M	490(DA)	60	0	450(129)	+	0	1+	1
39M	180(DO)	4	4,000	350(300)	+	1+	0	1
21M	600(DO)	156	12,600	450(390)	+	1+	1+	2
22F	570(DO)	12	0	380(283)	0	0	2+	2
35F	900(DO)	60	12,450	240(249)	+	2+	0	2
78M	280(DO)	10	0	300(245)	0	2+	0	2
12M	195(DO)	3	0	300(253)	+	1+	2+	3
15F	510(DO)	20	0	380(155)	+	2+	1+	3
29F	550(DO)	28	0	280(189)	+	1+	2+	3
49F	550(DO)	42	0	310(249)	+	2+	1+	3
5M	500(DO)	12	0	90(54)	+	2+	2+	4
33F	85(DO)	16	9,450	270(258)	0	2+	2+	4
11F	750(DO)	132	0	200(120)	+	3+	2+	5

irradiation; Obs = observed; PAOP = pulmonary artery occlusion pressure; Pred = predicted; PVH = pulmonary vascular hypertension; Rx = treatment; Sx = symptoms; + = present; 0 = absent.

In contrast to the previous 13 patients, histologic signs of cardiotoxicity were absent from multiple sections of myocardium in 7 of the 20 patients with clinical signs of drug toxicity (*Table I*). These 7 patients included 5 patients with and 2 without cavity dilatation. The 7 patients in whom clinical evidence of anthracycline cardiotoxicity was *not* associated with histologic abnormalities ranged in age from 5 to 61 years. Four received up to 630 mg/m² of daunorubicin, while 3 received 210 to 500 mg/m² of doxorubicin. All had evidence on physical examination of congestive heart failure. On chest radiograms, signs of pulmonary venous hypertension were present in all, and 5 of 7 had an enlarged cardiac silhouette. Two patients had abnormal echocardiograms, 1 had abnormal systolic time intervals, and 4 had elevated venous pressures.

Patients without clinical evidence of drug toxicity: Of the 64 patients, 44 (69%) had no clinical signs of cardiotoxicity. These patients (23 males, 21 females) ranged in age from 2 to 70 years (average 44).

Three of these 44 patients had >50 ml of fluid in the pericardial sac (500, 400, and 100), while in 3 others the pericardial space was obilterated by dense, fibrous adhesions. One of the former 3 patients and all of the latter 3 had received >4,900 rads of mediastinal irradiation. The average heart weight, excluding 2 children, was 278 g (range 105 to 450). In 29 patients, the observed heart weight exceeded the predicted heart weight by an average of 65 g. Biventricular dilatation was observed in 4 patients, and mild left ventricular enlargement in 2. Left ventricular mural thrombus was found in 1 patient with no history of peripheral embolic events.

Histologic signs of cardiotoxicity were observed in 23 (52%) of the 44 patients, despite the fact that none of these 44 patients had clinical evidence of anthracycline cardiotoxicity (Table II). In 15 of the 23 patients, the histologic findings were limited to a mild degree (combined score 1/6) of vacuolization (14 patients) or myofibrillar dropout (1 patient). In the remaining 8 patients, however, more extensive morphologic changes were noted: 4 patients received combined scores of 2/6 for histologic cardiotoxicity.

TABLE II Relation of Clinical Toxicity to Type and Extent of Morphologic Toxicity

Clinical Toxicity	Patients (n)	Type and Extent of Morphologic Toxicity: Myocardial Vacuoles 0	1	2	3	Myofibrillar Loss 0	1	2	3
+	20	9	4	6	1	10	4	6	0
0	44	22	17	3	2	37	7	0	0
Totals									
n	64	31	21	9	3	47	11	6	0
%	. . .	48	33	14	5	74	17	9	0

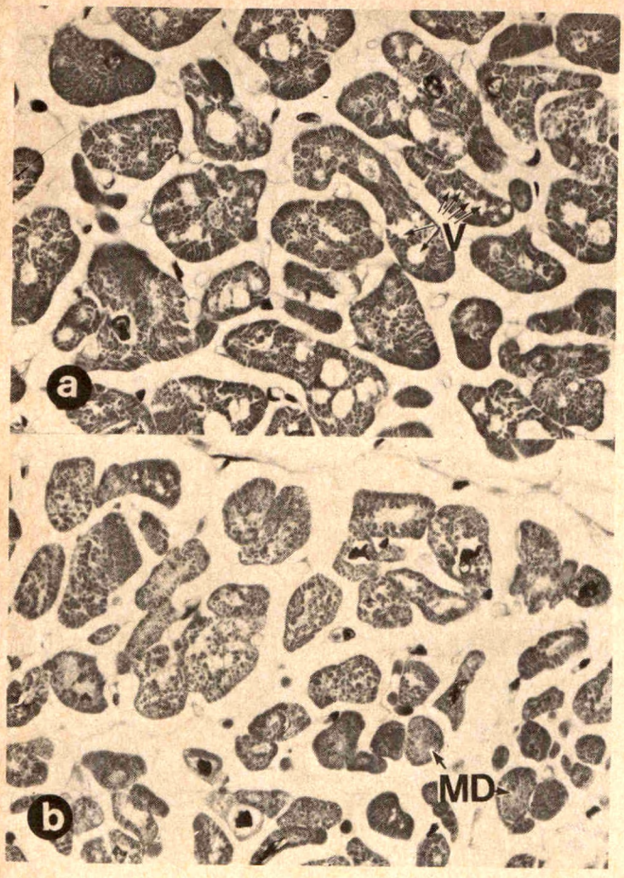

FIGURE 1. Findings used to score the extent of histologic cardiotoxicity: (**a**) vacuolization (V) of cardiac muscle cells, and (**b**) myofibrillar dropout (MD). This patient (15-year-old girl, Table I) received a histologic toxicity score of 3 (2+ vacuolization, 1+ myofibrillar dropout). (Hematoxylin and eosin stain; magnification ×500, reduced 33%.)

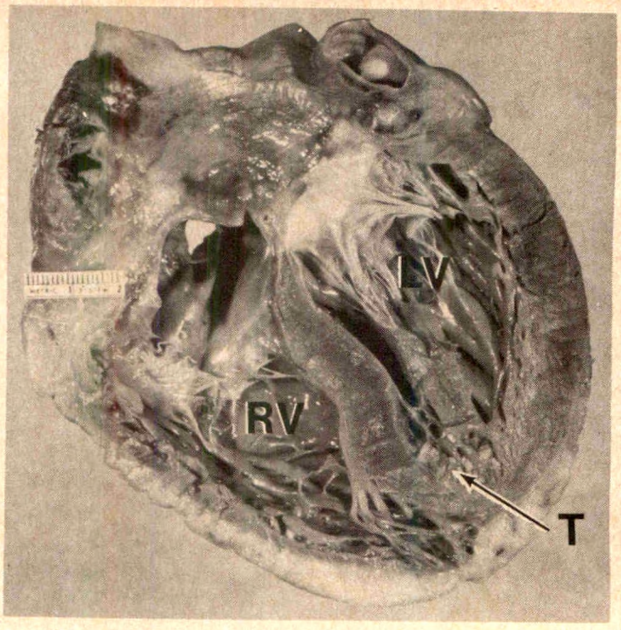

FIGURE 2. Biventricular cavity dilatation in 15-year-old girl (Table I) with clinical and histologic evidence of anthracycline cardiotoxicity. The apical portion of the dilated left ventricle (LV) contains antemortem thrombus (T). RV = right ventricle.

Patients grouped according to final (combined) scores for histologic cardiotoxicity (Fig. 3): The entire study group of 64 patients was analyzed from the standpoint of the combined score for histologic toxicity. Twenty-eight patients had a combined score of 0; 7 had clinical signs of toxicity while 21 did not. Seventeen patients received a histologic score of 1; clinical toxicity was present in 2 patients and absent in 15. Eight patients received a histologic score of 2; clinical toxicity was present in 4 and absent in 4. Seven patients received a histologic score of 3; 4 had clinical toxicity and 3 did not. Three patients received a histologic score of 4; 2 had clinical toxicity and 1 did not. Only 1 patient had a histologic score of 5 and this patient had overt clinical cardiotoxicity.

Relation between clinical cardiotoxicity and gross and histologic signs of toxicity (Fig. 4): Of the total 64 patients, 18 had neither clinical or structural evidence of cardiotoxicity. In 36 patients, histologic signs of toxicity were observed. Of these, 23 had no clinical evidence of toxicity, including 4 with dilated ventricles. Three patients had both clinical and histologic signs of toxicity unassociated with ventricular cavity dilatation. A complete "triad" of clinical, gross anatomic, and histologic signs of cardiotoxicity was observed in only 10 patients.

Of the remaining 10 patients of the study group of 64, 3 had ventricular cavity dilatation without histologic or clinical evidence of cardiotoxicity, 5 had clinical toxicity and cavity dilatation without histologic evidence of toxicity, and 2 had clinical signs of toxicity unassociated with either gross or histologic signs of toxicity. Thus, in 8 patients, cavity dilatation was not associated with histologic abnormalities.

Finally, in the entire study group of 64 patients, 20 had clinical signs of toxicity, and 2 of these patients showed no evidence of either cavity dilatation or histologic abnormalities. In 1, clinical evidence of toxicity consisted of jugular venous distention, inspiratory rales, and an S_3 gallop sound on physical examination; cardiomegaly and pulmonary venous hypertension on chest radiogram; and a central venous pressure of 20 mm Hg. The second patient also had an S_3 gallop sound, and cardiomegaly and pulmonary venous hypertension on chest radiogram. Both patients received treatment with digoxin and diuretics and 1 improved. Neither patient had pericardial fluid at necropsy.

The sensitivity of the histologic necropsy examination was calculated as follows: Patients with clinical and histologic toxicity/(patients with cardiotoxicity and histologic toxicity) + (patients with clinical toxicity without histologic toxicity) = 13/(13 + 7) = 0.65. The specificity of histologic necropsy examination was calculated as follows: Patients without clinical toxicity and without histologic toxicity/(patients without clinical toxicity and without histologic toxicity) + (patients with histologic toxicity without clinical toxicity) = 21/(21 + 23) = 0.48. The predictive value of the finding of his-

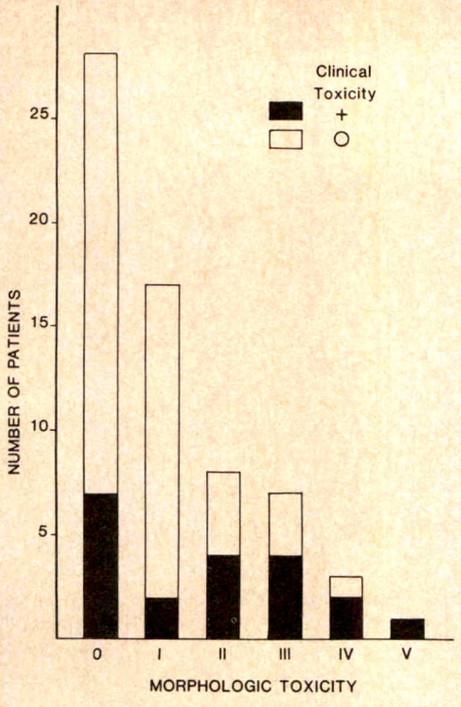

FIGURE 3. Number of patients with and without clinical evidence of cardiac toxicity in each category of histologic toxicity (see text for histologic toxicity grading system).

tologic toxicity was calculated as follows: Patients with clinical and histologic toxicity/(patients with clinical and histologic toxicity) + (patients with histologic toxicity without clinical toxicity) = 13/(13 + 23) = 0.36. This predictive value when tested proved not significantly different from random variation in toxicity (chi-square = 0.91, p >0.30).

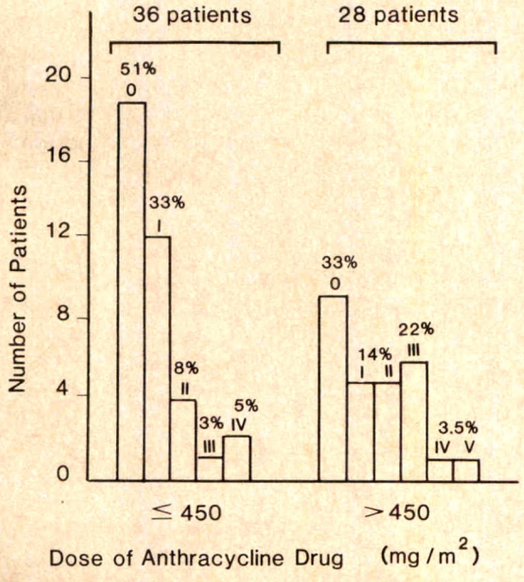

FIGURE 5. Scores for histologic toxicity grouped according to cumulative dose of anthracycline drug administered (≤450 or >450 mg/m²).

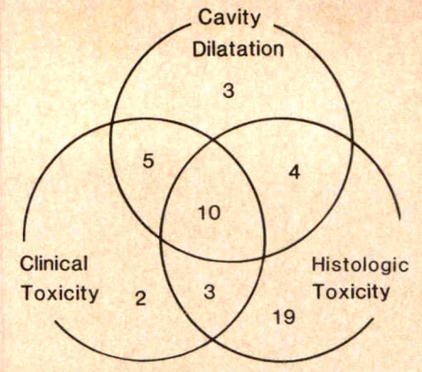

FIGURE 4. Relation of clinical cardiotoxicity to gross and histologic signs of cardiotoxicity. (Of the total 64 patients, 18 had neither clinical toxicity, cavity dilatation, nor morphologic toxicity and are not represented in this figure.)

Histologic toxicity as a function of cumulative dose of anthracycline drug: The relation between the extent of histologic signs of cardiotoxicity and the cumulative dose in mg/m² of anthracycline is illustrated in Figure 5. Of the 28 patients who received anthracycline therapy >450 mg/m², 13 (46%) had histologic scores of 2 to 5; in contrast, of 36 patients who received anthracycline therapy <450 mg/m², only 6 (17%) had histologic scores of ≥2 (p = 0.0097). Nevertheless, extensive histologic abnormalities were not limited to patients treated with >450 mg/m² of drugs: One patient treated with 100 mg/m² received a histologic toxicity score of 4 and had clinical signs of toxicity; 3 patients

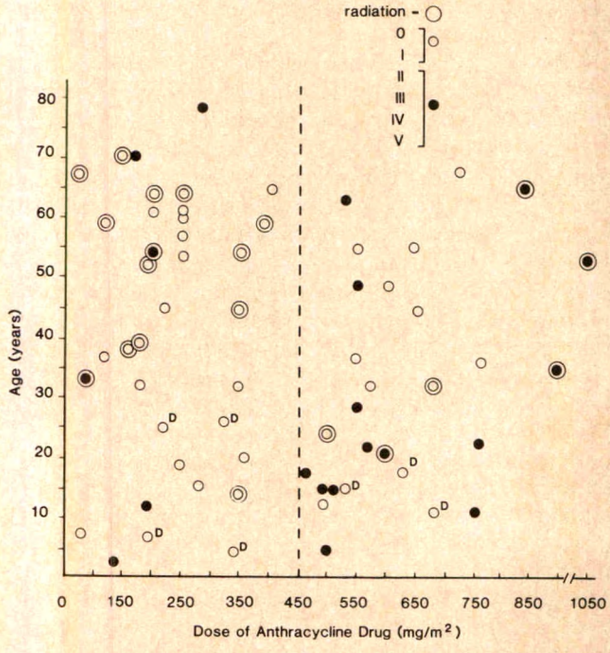

FIGURE 6. Morphologic toxicity as a function of cumulative dose of anthracycline drug, mediastinal irradiation, and age. All but 2 of the patients with scores of II to V received >450 mg/m², mediastinal irradiation, or were ≥70 years of age.

TABLE III Distribution of Histologic Changes (Morphologic Toxicity) in the Ventricular Walls of the Heart in 64 Necropsy Patients

Portion of Heart	Sections Examined (n)	Final Grade of Morphologic Toxicity						Nonrepresentative Sections
		0	I	II	III	IV	V	
Left ventricular free wall	62	26	14	8	7	3	1	3
Ventricular septum	36	12	7	6	5	0	1	5
Right ventricular free wall	50	22	7	3	5	3	1	9
Totals								
n	148	60	28	17	17	6	3	17
%	...	41	19	11	11	4	1	12

treated with 100 to 200 mg/m^2 received histologic toxicity scores of 2, 3, and 4, respectively, and 1 had clinical signs of toxicity; 2 patients treated with 200 to 300 mg/m^2 received a histologic toxicity score of 2.

Histologic toxicity as a function of cumulative drug, dose, age, and mediastinal irradiation: The effects of increasing age and mediastinal irradiation, in combination with cumulative drug dose, are illustrated in Figure 6. Of the 19 patients with combined histologic scores of 2 through 5, 13 received anthracycline therapy >450 mg/m^2. Of the 6 patients with extensive histologic changes who received <450 mg/m^2 of drug, 2 were treated with mediastinal irradiation (5,800 and 9,450 rads, respectively), and 2 were ≥70 years of age. Thus, all but 2 patients, in whom extensive histologic signs of anthracycline cardiotoxicity were recognized at necropsy, received >450 mg/m^2 of anthracycline therapy, or received combined mediastinal irradiation, or were ≥70 years of age.

Distribution of histologic abnormalities: The distribution of the histologic changes representing anthracycline cardiotoxicity is shown in Table III. Of 62 sections of left ventricular free wall from 64 patients, only 3 sections (5%) demonstrated histologic toxicity of lesser severity than was recognized in sections from either the ventricular septum or right ventricular free wall. Of 36 sections of ventricular septum taken from the 64 patients, only 5 (14%) were not representative of histologic lesions observed in sections taken from other sites of the myocardium. Of 50 sections taken from the right ventricular free wall, 9 (18%) were nonrepresentative. In those cases in which histologic toxicity was most extensive (histologic toxicity scores of 3, 4, and 5), these lesions were seen on sections taken from all 3 sites, that is, the right and left ventricular free walls and ventricular septum. The lesions corresponding to a histotoxicity score of 1 or 2 were more variable in distribution: In patients receiving a score of 1 or 2, the histologic abnormality was present in the left ventricle in 82 and 100%, respectively; in the ventricular septum in 64 and 64%; and in the right ventricular free wall in 54 and 50%.

Electrocardiographic findings in patients with and without clinical signs of drug toxicity: Electrocardiograms recorded between the time of onset of symptoms and the time of death were available in 9 of the 20 patients with clinical evidence of anthracycline toxicity. Two of the 9 patients had diminished amplitude of the QRS complex ("low voltage": ΣQRS amplitude [leads I, II, and III] ≤15 mm); in 1 of these 2 patients plus 1 other of the 9 patients, serial recordings demonstrated >30% diminution of the summated amplitude of the QRS complex in the limb leads. Pericardial heart disease was responsible for low voltage in only 1 of these patients. The mean cardiac weight of the 3 patients with reduced electrocardiographic QRS voltage was 248 g; the mean cardiac weight of the remaining 6 patients was 345 g.

Of the total group of 40 patients without clinical evidence of drug toxicity, 35 had electrocardiograms that were available for review: 11 (13%) had low voltage, including 1 with >30% diminution of the summated limb lead QRS amplitude on serial recordings. Their mean heart weight was 286 g, and none had pericardial heart disease, myxedema, cardiac amyloidosis, or hemochromatosis.

As a group, the 14 patients with low voltage and/or serial diminution in summated QRS amplitude did not differ significantly from the 30 patients with normal amplitude QRS complexes in terms of histologic findings: Vacuolar lesions were seen in 30% of the patients with and in 58% of the patients without low voltage; myofibrillar dropout in 20% of those with and in 28% of those without low voltage; interstitial fibrosis in 15% of those with and in 17% of those without low voltage; and attenuated myocytes ("fiber thinning") in 45% of the patients with versus 47% of those without low voltage.

Discussion

Anthracycline-induced cardiomyopathy was first reported by Tan et al[9] in 1967 in a 16-year-old girl treated with daunorubicin. Subsequent reports[10–14] confirmed the potential cardiotoxicity of daunorubicin and its derivative compound, doxorubicin. In the first detailed account of the morphologic findings of anthracycline-induced cardiomyopathy, Lefrak et al[5] described 2 patients in whom necropsy examination disclosed gross anatomic findings of biventricular dilatation with cavitary thrombus and histologic findings consisting of cytoplasmic hyaline transformation and cytoplasmic vacuolization. In both patients, clinical signs of a dilated cardiomyopathy had developed after they had received 720 and 825 mg/m^2 of doxorubicin.

Cortes et al[7] subsequently studied at necropsy 51 patients with doxorubicin, 17 (33%) of whom had signs of "toxic cardiopathy," defined as a combination of "intracellular edema, intracellular vacuolization, and myocardial fibrosis"; 5 had had congestive heart failure before death, and the remaining 12 never had overt cardiac failure.

Subsequent to these early necropsy observations, most published information regarding morphologic findings in patients receiving anthracycline drugs has been derived from analysis of myocardial biopsy specimens obtained from patients undergoing anthracycline chemotherapy.[4] Interest in this technique developed principally from 2 observations: (1) Although the development of anthracycline cardiotoxicity in general correlated with cumulative drug dose, in certain patients serious cardiotoxicity developed at relatively low doses,[15–19] while others, clearly in need of continuing chemotherapy, tolerated higher doses of the drug without adverse effects.[20] (2) Noninvasive methods contemporary to the early 1970s (electrocardiography, systolic-time intervals, echocardiography) proved unreliable for detecting latent, subclinical cardiac toxicity.[21–26] Thus, it was hoped that evaluation of serial biopsies might detect signs of potential cardiotoxicity before the time when cardiotoxicity became inevitable, and furthermore that biopsy analysis might predict how much longer a given patient could safely tolerate continued administration of anthracycline therapy.

The present study was designed to evaluate the correlation between clinical and morphologic signs of anthracycline cardiac toxicity in patients studied at necropsy. Examination of necropsy specimens eliminates the potential pitfalls posed by biopsy specimens, particularly the small size of tissue specimen,[27,28] limitation of sampling to subendomyocardial myocardium, and access to only 1 cardiac ventricle.[29] In addition, we hoped to extend the experience of Cortes et al[7] by (1) evaluating the pathologic material without knowledge of the clinical history, and (2) by establishing more rigid criteria for the definition of clinical and histologic signs of cardiotoxicity.

The present investigation suggests that prediction of clinical anthracycline cardiotoxicity on the basis of histologic changes is uncertain, because correlation between morphologic and functional changes is imperfect. Histologic signs of anthracycline cardiotoxicity may be absent, despite unequivocal clinical signs of a dilated cardiomyopathy: this situation was observed in 7 (35%) of our 20 patients. This finding has 3 important implications. The first, regarding therapy, is that in these 7 patients, an endomyocardial biopsy performed before the development of overt congestive heart failure would have suggested that treatment with anthracycline drugs could be continued safely. The second is that at least some of the "false-negative" results described in patients studied by the biopsy technique[22] are unlikely to have resulted simply from sampling errors. The third is that myofibrillar dropout and dilatation of the sarcoplasmic reticulum are not the only factors involved in the pathogenesis of anthracycline-induced cardiac failure. The concept that such failure is simply the result of structural damage to tissue represents an oversimplification of a very complex series of morphologic and biochemical changes.

The counterpart of the foregoing findings is that histologic signs of cardiotoxicity may be present without clinical signs of cardiac dysfunction: this situation was observed in 23 (52%) of 44 patients in the present report. Histologic signs of toxicity unassociated with clinical toxicity have been observed frequently in patients studied by endomyocardial biopsy, and, if extensive, have been interpreted as a contraindication to continued administration of anthracycline chemotherapy in these patients. The finding of morphologic toxicity in an asymptomatic patient—in the biopsy and, now, necropsy experience—suggests that such subclinical morphologic alteration may be the basis for the development of latent cardiac dysfunction described in long-term survivors of anthracycline therapy.[30,31] In nonhuman animal models of anthracycline toxicity, delayed development of cardiomyopathy has been observed as long as 6 months after discontinuation of therapy, and has been interpreted as evidence that the myocardial effects of anthracycline compounds are cumulative and irreversible.[32]

The serious discrepancies between morphologic and clinical evidence of toxicity found in the present investigation suggests that morphologic monitoring of patients receiving anthracycline drugs is of limited value for predicting the development of anthracycline cardiomyopathy. In contrast, physiologic evaluation of the cardiac response to exercise[26,31,33] or increased afterload[34] may improve the sensitivity of monitoring such patients for clinical evidence of latent cardiotoxicity. Long-term follow-up of such patients will determine whether such latent toxicity ultimately progresses to overt congestive heart failure.

Because this was a retrospective study and necropsy material from these patients had not been routinely preserved in glutaraldehyde fixative, examination of material was by necessity limited to gross anatomic and light microscopic studies. Nevertheless, as has been pointed out before, the morphologic lesions of anthracycline toxicity are evident by light microscopy.[27]

Electrocardiographic changes (low voltage or serial reduction $\geq$30% in limb lead voltage) previously proposed as evidence of anthracycline cardiotoxicity[35] correlated poorly with signs of morphologic toxicity in our patients, a finding noted previously by others.[23,36] The finding of low voltage was related to cardiac atrophy in patients with systemic cachexia, rather than to drug toxicity. The finding that cardiac atrophy frequently forms the morphologic basis for diminished QRS amplitude in such patients[37] makes this electrocardiographic feature particularly unsuitable for monitoring patients likely to be cachectic by virtue of their systemic illness.

Finally, our findings confirm observations made previously by Von Hoff,[2] Bristow,[33] and Billingham[38] regarding "risk factors" for anthracycline cardiotoxicity. Extensive morphologic toxicity was observed, with 2 exceptions, only in patients treated with >450 mg/m^2 of drug, or in patients in whom a smaller dose was ad-

ministered in association with mediastinal irradiation or to a patient ≥70 years of age. These findings support the concept of empiric limitation of total dose of drug, if possible, to <450 mg/m^2, and to an even smaller total in patients likely to receive mediastinal irradiation and in patients ≥70 years of age. Nevertheless, the finding of clinical or morphologic toxicity in patients treated with lower total doses of drug unassociated with mediastinal irradiation or advanced age suggests that empiric limitation of total dose of anthracycline is not by itself adequate to protect against the cardiotoxic effects of these drugs and mandates some form of associated monitoring.

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1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinylchloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,™ an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS
TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility
No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy
Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS
The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE
Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION
(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION
TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED
NDC 0094-0090-10. 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

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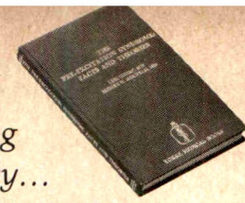

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

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Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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Mexiletine for Control of Drug-Resistant Ventricular Tachycardia: Clinical and Electrophysiologic Results in 44 Patients

LAWRENCE E. WASPE, MD,* HARVEY L. WAXMAN, MD, ALFRED E. BUXTON, MD,† and MARK E. JOSEPHSON, MD‡

The antiarrhythmic efficacy of mexiletine was evaluated in 44 patients with drug-resistant ventricular tachyarrhythmias. In 33 of these patients, the efficacy of mexiletine was assessed on the basis of the results of programmed ventricular stimulation. Mexiletine did not alter the ventricular effective refractory period, the Q-Tc interval, or the methods of tachyarrhythmia induction and termination during programmed stimulation. The mean cycle length of ventricular tachycardia (VT) increased from 270 ± 49 to 313 ± 80 ms in 21 patients in whom VT remained inducible on mexiletine alone ($p < 0.002$). Overall, VT remained inducible with methods similar to control (no drugs) inductions in 25 patients receiving mexiletine alone or in combination with a type I agent. VT induction was prevented in only 8 patients, 3 on mexiletine alone and 5 receiving mexiletine combined with another drug. Mexiletine alone (in 2 patients) or with another agent (in 3) suppressed clinical recurrence of VT in an additional 5 of 11 patients who did not undergo electrophysiologic study. These 13 patients were discharged on mexiletine alone (5 patients) or in combination with other drugs (8 patients), and remained arrhythmia-free over a mean follow-up period of 7.7 ± 4.1 months. Adverse effects occurred in 27 of 44 patients (61%) and were gastrointestinal in 17 and/or neurologic in 22. The drug was discontinued because of adverse effects in 6 patients (14%). Thus, mexiletine has limited efficacy when used alone, but when combined with other drugs it may be useful in up to 30% of patients with drug-resistant ventricular arrhythmias. Adverse effects are relatively common.

Mexiletine, a class I antiarrhythmic agent structurally similar to lidocaine, has been undergoing clinical investigation in Europe since 1971.[1] Currently, it is being evaluated in the United States for treatment of ventricular arrhythmias. Mexiletine has been effective in suppressing ventricular arrhythmias associated with acute and chronic ischemic heart disease,[2–7] in other types of heart disease,[1,5,8] and in patients with apparently normal hearts.[1,2,4,5] Studies indicate that mexiletine can suppress ventricular arrhythmias that have been refractory to management with conventional antiarrhythmic agents.[1,5,7,9,10] Because mexiletine has a plasma half-life of 7 to 18 hours,[7,11,12] allowing for convenient dosing intervals, the drug may be useful in the long-term management of ventricular arrhythmias.[1,4,5,7]

Most studies examining mexiletine used criteria of ventricular premature complex suppression or abolition of clinical recurrence of ventricular arrhythmia to assess its efficacy.[1–9] Few studies have primarily used serial electrophysiologic testing to evaluate the usefulness of mexiletine in treating ventricular tachyarrhythmias.[10,13] In this report we present our clinical and electrophysiologic experience with mexiletine in 44 patients with ventricular tachycardia (VT) or ventricular fibrillation (VF) resistant to treatment with conventional agents.

From the Clinical Electrophysiology Laboratory, Hospital of the University of Pennsylvania, Cardiovascular Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. This work was supported in part by grants from the American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia, Pennsylvania, and Grant HL24278 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received June 22, 1982; revised manuscript received and accepted November 8, 1982.

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Methods

Study patients: The study group consisted of 44 patients, 28 men and 16 women aged 28 to 79 years (mean 56 ± 13), with a history of VT or cardiac arrest whose arrhythmias were refractory to treatment with conventional drugs or other experimental antiarrhythmic agents. Twenty-nine patients had recurrent sustained VT, 7 had cardiac arrest, VF was the first arrhythmia documented, and 8 had recurrent episodes of nonsustained VT associated with syncope or near-syncope.

All patients had 1 to >25 episodes (mean 6 ± 4.9) of clinical ventricular arrhythmia before mexiletine therapy. Twenty patients (45%) had ≥1 cardiac arrests and 6 patients had ≥1 syncopal episodes. Thirty-two patients (73%) required 1 to >25 cardioversions for termination of sustained VT or VF.

Previous antiarrhythmic therapy consisted of the following: a mean of 3.4 ± 1 (range 1 to 5) conventional agents per patient, 1 to 3 drug combinations per patient in 20 cases, and at least 1 other experimental agent in 10 patients. *Failure of previous drug therapy* was defined as a documented recurrence of the patient's clinical arrhythmia, the occurrence of an unacceptable adverse effect, or continued inducibility of the arrhythmia during electrophysiologic testing.

All patients except 2 had evidence of organic heart disease including coronary artery disease in 32, idiopathic cardiomyopathy in 4, mitral valve prolapse in 2, hypertensive cardiovascular disease in 1, aortic stenosis with aortic valve replacement in 1, left ventricular aneurysm in the absence of coronary artery disease in 1, and arrhythmogenic right ventricular dysplasia in 1.

All patients with coronary artery disease had had ≥1 myocardial infarction at least 1 month before mexiletine testing. Eighteen of the 32 patients with coronary artery disease had a left ventricular aneurysm. Three patients had previous left ventricular aneurysmectomy either for attempted control of ventricular tachycardia or for hemodynamic indications.

Left ventricular ejection fraction was determined in 22 patients by cardiac catheterization and in 18 patients by nuclear blood pool scan. The mean ejection fraction was 42 ± 18% (range 15 to 85). In 30 of 32 patients with coronary artery disease, the mean ejection fraction was 38 ± 15% (range 15 to 67).

Electrophysiologic testing: Programmed ventricular stimulation was performed, using the protocol to be described, during 1 or more phases of drug evaluation in 40 of the 44 patients. For our study, there were as many as 3 phases of evaluation: (1) a control study on no antiarrhythmic medications, (2) a study on mexiletine alone, and (3) a study on mexiletine in combination with another antiarrhythmic agent. Most patients had additional electrophysiologic tests to evaluate other antiarrhythmic agents that were tried during the course of their therapy.

Electrophysiologic testing was performed with the patient in a postabsorptive, nonsedated state after written informed consent had been obtained.[14] Three or 4 multipolar electrode catheters were inserted percutaneously into femoral or antecubital veins and positioned under fluoroscopic guidance at the high right atrium, the atrioventricular junction for His bundle recording, the coronary sinus, and the right ventricular apex. Programmed stimulation was performed using pulses of 1-ms duration at twice diastolic threshold using a custom-designed programmable stimulator and an optically isolated constant current source (Bloom Associates, Narberth, Pennsylvania).

The stimulation protocol during control and all subsequent studies consisted of the introduction of single, double, and triple extrastimuli during sinus rhythm and ventricular pacing at multiple cycle lengths (600 to 400 ms) and bursts of rapid pacing (400 to 250 ms for 5 to 30 seconds) at the right ventricular apex. If VT was not induced, this protocol was repeated with the stimulating catheter at the right ventricular outflow tract. One catheter was routinely used during follow-up testing. Ventricular tachycardia was defined as *sustained* if it persisted for ≥30 seconds or required termination in less time because of hemodynamic compromise. Ventricular tachycardia was considered *nonsustained* if its duration was between 6 beats and 30 seconds, and termination was spontaneous. A *satisfactory response* to programmed stimulation was defined as failure to induce any ventricular tachyarrhythmia with the foregoing methods, or induction of only well-tolerated nonsustained VT in the course of the complete stimulation protocol.

Mexiletine administration: Mexiletine was given orally at a daily dosage of 300 to 1,200 mg in 3 divided doses. The mean maximal dose employed was 250 ± 75 mg every 8 hours. No loading dose was given. Because plasma concentrations of mexiletine were not readily available, the patients were routinely begun on 200 mg every 8 hours and the dosage was titrated upward (or downward in 2 cases) until dose-related toxicity occurred or a maximal daily dose of 1,200 mg was reached.

Electrophysiologic testing was performed to evaluate mexiletine after patients had been maintained on a maximally tolerated dose for 3 to 7 days. When combined oral therapy was evaluated by programmed stimulation, patients were maintained on a maximally tolerated dose of the additional antiarrhythmic drug for 3 to 5 days before testing. When intravenous procainamide was added to mexiletine, repeat testing was performed on the same day. Patients maintained on digoxin or propranolol, or both, for heart failure, atrial arrhythmias, or angina remained at a constant dose throughout the period of study.

In some cases, 24-hour Holter monitor recordings were obtained off medication and again on mexiletine for correlation with the results of programmed stimulation. A *therapeutic effect* attributable to mexiletine was defined as a reduction in ventricular premature complex frequency by more than 83% in comparison with the control monitoring period.[15]

The criteria by which the efficacy of mexiletine was assessed were the following: *effective* if sustained ventricular tachycardia could not be induced by programmed stimulation, or there were no spontaneous recurrences of the patient's clinical ventricular arrhythmia during the follow-up period, or both; *partially effective* if another medication that was ineffective alone was effective in combination with mexiletine, or if the number of spontaneous recurrences of a well tolerated arrhythmia decreased; and *ineffective* if arrhythmia recurrence was not favorably altered, and the patient's clinical ventricular arrhythmia remained inducible on mexiletine or mexiletine in combination with another agent, or mexiletine had to be discontinued within a few days of therapy because of intolerable adverse effects (3 cases).

Patients discharged on mexiletine were followed up for symptomatic recurrence of arrhythmia as determined by interview of the patient during regular clinic visits and by periodic telephone questioning of the patient or his physician. In all instances, reported recurrences could be verified by electrocardiographic tracings taken in emergency rooms or recorded on ambulatory monitors.

Statistical analysis of the data was performed using the paired Student's t test and chi-square analysis with Yates correction where appropriate. Data are expressed as mean ± standard deviation unless otherwise noted.

TABLE I Effect of Mexiletine on Cycle Length of Induced Ventricular Tachycardia (VT)

	Control	Mexiletine	Mexiletine + Another Agent	p	n
VT cycle length (ms), all morphologies	270 ± 39	313 ± 80	. . .	<0.002	21
VT cycle length (ms), same morphology	278 ± 50	332 ± 81	. . .	<0.001	16
VT cycle length (ms), all morphologies	247 ± 53	. . .	373 ± 113	<0.001	23
VT cycle length (ms), same morphology	265 ± 48	. . .	387 ± 105	<0.001	13

Results

Electrophysiologic observations: *Inducibility: Control versus mexiletine studies:* Ventricular arrhythmias were inducible during a control study in 37 patients. Six patients had no control study because of frequent episodic or incessant VT, and 1 patient had no inducible ventricular tachyarrhythmia. Thirty-three patients with control studies underwent electrophysiologic testing on mexiletine (23 patients) and/or mexiletine in combination with another drug (25 patients). Patients were studied on mexiletine combined with other drugs when arrhythmias remained inducible on mexiletine (15 patients) or when other agents used alone failed to prevent arrhythmia induction (10 patients).

Among 23 patients who underwent programmed stimulation on mexiletine, the following arrhythmias were induced during control studies: sustained VT in 21 patients, and polymorphic VT (torsade de pointes) degenerating into VF in 2. On mexiletine, sustained VT remained inducible in 17 patients, and nonsustained VT was initiated in 6. The response to programmed stimulation was considered satisfactory in 3 patients whose nonsustained VT on mexiletine was well tolerated (see later).

Fifteen patients who failed electrophysiologic testing on mexiletine and 10 patients who initially failed testing on other drugs underwent programmed stimulation on combined therapy. The following agents were tested in combination with mexiletine: disopyramide (3 patients), procainamide (12), propranolol (1), quinidine (8), and amiodarone (1). During control studies sustained VT was induced in 23, polymorphic ventricular tachycardia (torsade de pointes) degenerating to VF in 1, and nonsustained VT in 1. When programmed stimulation was performed on combined therapy, 20 patients still had sustained VT, 4 had nonsustained VT, and 1 patient had no inducible arrhythmia. The response to electrophysiologic testing was considered satisfactory in the latter 5 patients (see later).

A total of 11 patients without control electrophysiologic tests who had adverse effects or spontaneous arrhythmia recurrences on mexiletine did not undergo electrophysiologic evaluation on mexiletine. Their response to mexiletine was evaluated on a clinical basis (see later).

Effect of mexiletine on cycle length, induction, and termination of VT (Table I, Fig. 1): Among 23 patients with electrophysiologic studies on no drugs and on mexiletine alone, sustained or nonsustained VT remained inducible, and the cycle lengths could be compared in 21. The mean cycle length was 270 ± 49 ms on no drugs as compared with 313 ± 80 ms on mexiletine ($p < 0.002$) (Fig. 1). In 16 of these 21 patients, a morphologically similar VT was induced during the control and mexiletine studies. The VT cycle length increased in these patients from 278 ± 50 ms to 332 ± 81 ms ($p < 0.001$).

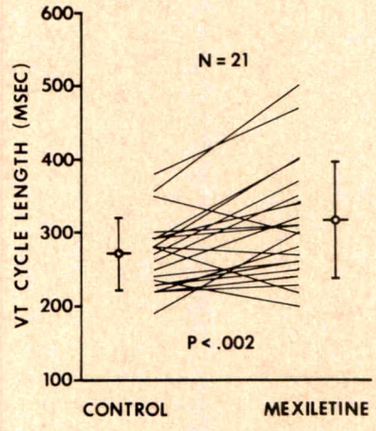

FIGURE 1. Effect of mexiletine on ventricular tachycardia (VT) cycle length. Mexiletine increased the mean cycle length of VT in 21 patients who had VT induced during control and mexiletine studies.

Among 24 patients with sustained or nonsustained VT induced on mexiletine in combination with another drug, cycle lengths could be compared with those in control studies in 23 patients. In these patients the tachycardia cycle length increased from 247 ± 53 ms during a control study to 373 ± 113 ms ($p < 0.001$). Thirteen patients had tachycardias of similar morphologies and demonstrated an increase in cycle length from 265 ± 48 ms during a control study to 387 ± 105 ms ($p < 0.001$). Patients in whom the morphologic characteristics of VT on mexiletine alone or in combination with other drugs differed from those of control studies had tachycardia configurations similar to control arrhythmias on at least 1 occasion during serial drug testing.

Among patients whose ventricular arrhythmias were inducible during control and treatment studies, mexiletine alone or in combination with other drugs did not alter the method of induction in any consistent manner. Similarly, there was no predictable change in the mode of termination.

TABLE II Mexiletine Efficacy in 44 Patients

	Effective (n = 3)	Partially Effective (n = 10)		Ineffective (n = 31)	
No EPS		5		6	
EPS results					
VT inducible					25
VT noninducible	3		5		
Follow-up					
Adverse effects			2	3	
Death		1*			
Recurrent VT		1†	1‡	3	
Other medical therapy					19
Surgery					6
Mex alone, no recurrence	3				
Mex + another agent, no recurrence		3	2		

* Mexiletine partially effective because of complete suppression of incessant VT for 3.5 months before death.
† Mexiletine in combination with another drug completely suppressed incessant VT for 5 months.
‡ Complete VT suppression for 4 months.
EPS = electrophysiologic study; Mex = mexiletine; VT = sustained ventricular tachycardia.

Effect of mexiletine on refractory period and Q-Tc: Ventricular refractory periods measured during a control study and during mexiletine therapy could be compared in 13 patients. Mexiletine had no significant effect on the refractory period measured at the right ventricular apex at a paced cycle length of 600 ms: 255 ± 18 ms (control) versus 259 ± 24 ms (mexiletine) ($p = 0.33$). Refractory periods could not be compared in all patients because the site or cycle length of stimulation, or both, were not identical in both studies, or because VT was induced before refractoriness was reached.

Standardized 12-lead electrocardiograms were available for comparison on no antiarrhythmic medications and on mexiletine in 26 patients. The Q-T interval corrected by Bazett's formula was not significantly altered by mexiletine administration: 434 ± 55 ms (control) versus 426 ± 43 ms (mexiletine) ($p = 0.2$).

Efficacy of mexiletine for control of ventricular arrhythmias (Table II): The clinical efficacy of mexiletine was assessed in all 44 patients. In 3, mexiletine was stopped in 3 to 11 days because of intolerable side effects. No programmed stimulation was performed before mexiletine discontinuation, and these patients have been grouped in the ineffective category. The results in 25 patients were judged ineffective by electrophysiologic testing, and another 3 patients were classified in the ineffective group because VT spontaneously recurred soon after mexiletine was begun. Mexiletine alone (5 patients) or in combination with another drug (8 patients) provided effective or partially effective therapy in 13 patients (30%). The drug was stopped in 1 of these patients within 5 days because of adverse effects. The remaining 12 patients were followed up a mean of 7.7 ± 4.1 months (range 2.4 to 15).

Effective group: Mexiletine alone provided effective therapy in 3 (7%) of 44 patients, all of whom had sustained VT in a control study and on multiple other antiarrhythmic medications. Programmed stimulation on mexiletine alone induced only brief episodes of well-tolerated nonsustained VT in each of these patients (6 to 69 complexes). The response to testing was considered satisfactory in the patient with 69 complexes of induced VT because it was well tolerated (cycle length 400 ms). This result was clearly superior to those obtained with all other drugs. Two patients are on 900 mg/day of mexiletine, and the third is taking 600 mg/day. No patient has had a recurrence of VT over 5.5, 11.5, and 15 months of follow-up, respectively.

Partially effective group: Mexiletine was partially effective in another 10 patients (23%). Used alone, mexiletine significantly reduced the spontaneous recurrence rate of VT in 2 patients. Ventricular tachycardia, which had been incessant, was completely suppressed in both for 3.5 and 5 months, respectively. One of these patients died suddenly at the end of 3.5 months of follow-up, but is considered in the partially effective category because of mexiletine's dramatic suppressive effect before her death. Ventricular tachycardia recurred after 5 months of complete suppression in the other patient and ultimately was controlled by amiodarone plus quinidine.

Mexiletine provided partially effective therapy when combined with a previously ineffective agent in 8 cases: (procainamide, 3; disopyramide, 2; quinidine, 2; and propranolol, 1). Five of these patients, all of whom had inducible sustained VT during a control study, underwent follow-up programmed stimulation. Only well-tolerated nonsustained VT could be induced in 4. No ventricular arrhythmia was inducible in the other patient. Mexiletine was considered partially effective in these patients because combined therapy prevented the induction of sustained VT during the complete programmed stimulation protocol. All but 1 of these patients were discharged on mexiletine in combination with another antiarrhythmic agent. Eventually, mexiletine was discontinued in 2 of these patients (1 before hospital discharge) because of adverse effects. Mexiletine was stopped in a third patient because sustained VT recurred after 4 months of total suppression. The 2 remaining patients have been free of arrhythmias for 10 and 13 months, respectively.

Mexiletine in combination with another drug was partially effective in 3 other patients who did not undergo follow-up ventricular stimulation. Before therapy 1 patient had incessant VT, 1 had monthly recurrences of sustained VT, and 1 had weekly episodes of nonsustained VT associated with syncope. On mexiletine plus quinidine, the patient with incessant VT had only 1 arrhythmia recurrence after 3.5 months. After an increase in the quinidine dose, this patient has been arrhythmia-free for an additional month. Combined therapy has completely suppressed ventricular arrhythmias in the remaining 2 patients over 3.5 and 8.5 months of follow-up.

Ineffective group: Mexiletine alone or in combination with another agent was ineffective in controlling arrhythmias in 31 of 44 patients (70%). In a total of 25 patients, ventricular tachycardia remained inducible on mexiletine alone (20 of 23) patients or in combination with another antiarrhythmic drug (20 of 25) patients. Six additional patients with no follow-up electrophys-

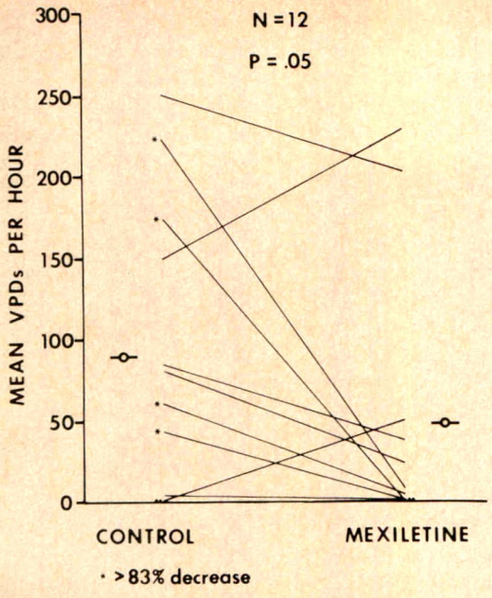

FIGURE 2. Effect of mexiletine on ventricular premature depolarization (VPD) frequency. Among 12 patients with 24-hour Holter monitors in the control state and while on mexiletine, 4 had a significant decrease in mean VPD frequency (>83%)[15] on mexiletine. Overall, the effect of mexiletine on ventricular ectopic activity was not significant (p = 0.05).

iologic testing were in the ineffective group. Three of these patients continued to have frequent clinical recurrences of VT on mexiletine alone or in combination with another drug. Mexiletine was ineffective in 3 others because of adverse effects requiring its discontinuation within 3 to 11 days.

There were 3 deaths among patients in the ineffective category. None was sudden or occurred while the patient was taking mexiletine. With 3 exceptions, the surviving 28 patients achieved satisfactory control of their ventricular arrhythmias with surgery or other experimental drugs. Ultimately, 3 patients were incompletely but best treated with conventional agents.

Results of 24-hour Holter monitoring (Fig. 2): Twenty-four-hour Holter monitors were available in 12 patients in the control state and while on mexiletine. Mexiletine decreased the mean number of ventricular premature complexes per hour from 89 ± 90 to 47 ± 81, but this was short of statistical significance (p = 0.053). Also, episodes of nonsustained VT recorded during control periods in 2 patients recurred during maximally tolerated mexiletine therapy. In 4 patients, however, a significant reduction in premature complex frequency (>83%)[15] did occur on mexiletine. Ten patients with monitoring data, including these 4, underwent electrophysiologic testing on mexiletine. Ventricular tachycardia remained inducible in 3 of the 4 patients with satisfactory Holter monitor results as well as in all 6 with inadequate results. Therefore, mexiletine efficacy as assessed by Holter monitoring in this small number of patients was limited and did not correlate with the response to programmed stimulation.

Adverse effects (Table III): Side effects developed in 27 patients (61%) while taking mexiletine, and were

TABLE III Adverse Effects

	Instances*		Reason for Drug† Discontinuation	Mean Time to Occurrence (days)
	n	%		
Gastrointestinal	17	39	2	. . .
Nausea	17	39	2	1.7 ± 1.0
Vomiting	6	14	2	1.8 ± 1.3
Neurologic	22	50	6	. . .
Lightheadedness	11	25	3	1.6 ± 1.1
Hand tremor	11	25	3	2.5 ± 1.6
Ataxia	9	20	4	1.9 ± 1.6
Confusion	2	5	0	1, 7
Blurred vision	1	2	0	4

* Patients often had more than 1 adverse effect.
† Multiple adverse effects occurred in all 6 patients requiring discontinuation of mexiletine.

severe enough to require discontinuation of the drug in 6 (14%). The mean 8 hourly dose at which adverse effects occurred was 274 ± 86 mg (range 100 to 400). This mean was not significantly different from that of the group without adverse effects (235 ± 61 mg, p >0.1) and represented the approximate median of the recommended dose range.[1–5,7,8,10,12]

Seventeen patients (39%) had gastrointestinal complaints on mexiletine. All became nauseated, and in 6 vomiting developed. With few exceptions, symptoms occurred within 1 to 4 days of mexiletine therapy, and were relieved when the 8 hourly mexiletine dose was decreased by 100 to 200 mg. In 2 patients, continued nausea and vomiting necessitated discontinuation of the drug on the third to the sixth day of treatment.

Neurologic symptoms were observed in 22 patients (50%). In order of frequency they were: lightheadedness (11), hand tremor (11), ataxia (9), confusion (2), and blurred vision (1). These symptoms also occurred early in the course of mexiletine therapy (1 to 7 days), and usually resolved with a 100 to 200 mg decrement in the 8 hourly dose. Persistent lightheadedness, ataxia, and/or tremor despite a decrease in dose was the primary or partial cause of mexiletine discontinuation in all 6 patients in whom the drug was stopped. Four patients were taking 900 mg/day, and 2 were taking 600 mg/day. Mexiletine was stopped within 11 days in 5 of 6 patients. The patients in whom confusion or blurred vision developed improved when the dose was reduced.

In 2 patients nausea and lightheadedness developed in the chronic phase of mexiletine therapy (2 to 10 months). Each had been on a stable dose of the drug. One patient improved with a dose reduction, but the other required discontinuation of mexiletine for symptom relief.

Discussion

Antiarrhythmic efficacy (Table II): We found that mexiletine provided effective or partially effective therapy for only 13 of 44 selected patients (30%) with drug-resistant VT or VF. Because several laboratories have shown that the results of electrophysiologic testing predict the long-term efficacy of antiarrhythmic agents,[16–18] the efficacy of mexiletine was evaluated principally on the basis of arrhythmia noninducibility during programmed stimulation. Of 33 patients so

tested, only 3 had no inducible sustained tachyarrhythmia on mexiletine alone, and 5 had no inducible sustained arrhythmia on mexiletine combined with other drugs. Mexiletine was classified as ineffective in 25 patients whose ventricular arrhythmias remained inducible. Mexiletine alone (in 2 patients) or in combination with other agents (in 3) suppressed clinical arrhythmia recurrences in 5 of 11 patients who did not undergo electrophysiologic testing. Therefore, these 5 patients and the 8 noninducible patients comprised the effective and partially effective groups discharged on a mexiletine regimen.

The resulting 30% efficacy rate must be further interpreted in light of the following considerations: (1) Among 13 patients discharged on mexiletine, only 5 were treated with mexiletine alone. Eight required the addition of another drug to achieve arrhythmia suppression. (2) The completely effective category consisted of only 3 patients who had no inducible sustained tachyarrhythmia on mexiletine alone. (3) Because the mean follow-up period was relatively short (7.7 ± 4.1 months), it is possible that the efficacy rate might have been lower over a longer term. (4) The efficacy of mexiletine was additionally limited during follow-up by the late death of 1 patient, late recurrences of VT in 2 patients, and by adverse effects requiring discontinuation of the drug in 2 others.

Comparison with other studies: On the basis of clinical arrhythmia suppression and reduction of premature complex frequency, other studies have reported satisfactory results in 30 to 95% of patients treated with mexiletine.[1–5,7,8,12] Two studies similar to ours in that they involved a drug-refractory population and used equivalent mexiletine doses found that VT was suppressed in 50 and 27% of patients, respectively.[7,12]

Two groups have evaluated the efficacy of mexiletine for drug-resistant ventricular arrhythmias using serial electrophysiologic testing.[10,13] DiMarco et al[10] found that mexiletine prevented the induction of VT in 42% of 41 patients evaluated by programmed stimulation. Among the patients with no inducible arrhythmias, 94% remained arrhythmia-free over a mean follow-up period of 1 year. However, Palileo et al[13] reported that sustained VT remained inducible on mexiletine in 9 of 10 patients they tested.

The overall efficacy rate observed in our study is between the extremes of the reports that evaluated mexiletine on the basis of clinical arrhythmia suppression or electrophysiologic testing. Studies in both categories dealt with a patient population similar to ours, and used comparable mexiletine doses. The high incidence of arrhythmia induction in our patients on mexiletine therapy agrees with the observations of Palileo et al.[13] Our results may have differed from those of DiMarco et al[10] because a more vigorous stimulation protocol was used. Our protocol included triple extrastimuli at 2 right ventricular sites in about one third of patients. Also, in contrast to the study of DiMarco et al,[10] our patient population did not include those with only repetitive ventricular responses which became noninducible on mexiletine therapy. We did not evaluate a sufficient number of patients solely on the basis of clinical arrhythmia suppression to make a comparison with those studies meaningful.

Electrophysiologic and 24-hour Holter monitor observations: Our findings that mexiletine significantly increased the cycle length of inducible VT, but had no effect on the ventricular effective refractory period or corrected Q-T interval have previously been noted.[7,8,13,19] As the present study emphasized the evaluation of mexiletine by programmed stimulation, only limited Holter monitor data were available. Mexiletine significantly decreased ventricular ectopic activity in a minority of our patients (4 of 12). Furthermore, significant ventricular premature complex suppression did not correlate with efficacy as assessed by programmed stimulation in these 4 patients.

Adverse effects: We observed a high incidence of adverse effects during mexiletine therapy (61%). These occurred at doses that were not significantly different from those of the group without side effects, and were similar to previously reported therapeutic dose ranges.[1–5,7,8,10,12] The untoward effects were gastrointestinal or neurologic in nature. They usually developed within the first week of therapy, and most commonly occurred within 48 hours of starting mexiletine therapy or increasing the dose. Adverse effects resolved in the majority of patients (21 of 27) by decreasing the dose and, therefore, appeared to be dose-related. We agree with others who have noted a narrow toxic to therapeutic ratio,[4,7,12] because dose adjustments that caused or relieved symptoms were small. The incidence of adverse effects reported with the use of mexiletine has ranged from 10 to 74%.[1–5,7,8,10,12] When used orally, symptoms were restricted to gastrointestinal and neurologic systems and, as in our study, occurred within the first several days of therapy.[10]

Implications: Our observations suggest that mexiletine alone or in combination with other drugs may be useful in the treatment of, at most, 30% of patients with ventricular arrhythmias resistant to conventional agents. In most patients (33), mexiletine was evaluated by electrophysiologic testing, with the assumption that this is predictive of long-term drug efficacy.[16–18] Only 8 patients (24%) had no inducible sustained arrhythmias on a mexiletine regimen. Of these, only 3 (9%) had no inducible sustained arrhythmia on mexiletine alone. Because electrophysiologic testing was carried out after several days of a maximally tolerated dose of mexiletine, the efficacy we observed was probably the highest attainable with our stimulation protocol. A study based more on clinical arrhythmia suppression and Holter monitoring might have yielded different results. However, when the small group (11 patients) we evaluated on the basis of clinical arrhythmia suppression was compared with the group evaluated by programmed stimulation, there was no significant difference in overall efficacy (5 of 11 versus 8 of 33, chi-square with Yates = 0.910, $p > 0.30$). When the use of mexiletine alone is considered, our data indicate a limited antiarrhythmic effect. Its administration is associated with a relatively high incidence of adverse effects. Therefore,

mexiletine appears to have only moderate usefulness in the treatment of patients with recurrent drug-resistant ventricular tachyarrhythmias.

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Possible Contribution of Encainide Metabolites to the Long-Term Antiarrhythmic Efficacy of Encainide

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To establish long-term efficacy and the relation between drug plasma concentration and antiarrhythmic response, 12 patients with encainide-responsive frequent complex ventricular ectopic activity underwent 1 year of therapy with encainide. Twenty-four hour ambulatory electrocardiograms were obtained at baseline and every 2 months. Drug withdrawal with concomitant plasma sampling and electrocardiographic monitoring was performed at 6 and 12 months. Average group premature ventricular contraction (PVC) suppression during the year was 97 to 99%, with nearly total suppression of pairs and salvos. The most common adverse effects were transient visual disturbances and dizziness or lightheadedness. During a dose interval (6 to 12 hours) the concentration of encainide metabolites exceeded that of encainide by several-fold. The median time of arrhythmia return after drug withdrawal was 12 to 14 hours. At the time of arrhythmia return encainide was generally no longer detectable but the average concentration of O-demethylencainide and 3 methoxy-O-demethylencainide was 72 ± 49 and 172 ± 74 ng/ml, respectively. It is concluded that encainide therapy is extremely effective for continuous long-term suppression of complex ventricular arrhythmias and its metabolites contribute significantly to its antiarrhythmic action during chronic oral therapy.

Encainide is a new antiarrhythmic drug that is extremely effective for suppression of ventricular ectopic activity[1–4] and is useful for treating some patients with recurrent life-threatening ventricular tachyarrhythmias.[5] Although encainide has a short half-life of 1.9 to 3.8 hours,[1] it is effective in most patients when given on a 6 to 8 hour dosing regimen. A wide toxic to therapeutic ratio as well as the possibility of pharmacologically active metabolites have been postulated to explain this finding.[2] Encainide is known to undergo extensive metabolism to a number of compounds, including O-demethylencainide (ODE) and 3-methoxy-O-demethylencainide (MODE). Preliminary animal data[6] suggest that these compounds have pharmacologic activity and several indirect observations suggest that they contribute to encainide's antiarrhythmic activity in man. In a previous study[2] comparing the antiarrhythmic action of single oral and intravenous doses of encainide, we found that the plasma concentration of encainide required for arrhythmia suppression was higher after intravenous than after oral administration. This study was performed using a radioimmunoassay which measures primarily encainide and not its metabolites.[7] Jackman et al[8] presented data indicating that encainide's electrophysiologic effects after multiple oral doses are different from those measured after acute intravenous dosing.[9] The observations from both of these studies are consistent with the formation of pharmacologically active metabolites in greater quantities after oral as compared with intravenous dosing. The present study was initially designed to examine the long-term efficacy and safety of encainide in patients with chronic ventricular ectopic beats and to examine simultaneously the relation between encainide plasma concentration and its antiarrhythmic effects. Development of a new high pressure liquid chromatographic assay[7,10] which measures both unchanged encainide as well as its metabolites (Fig. 1) permitted us to relate arrhythmia suppression during chronic oral therapy to the plasma concentration of both encainide and its metabolites.

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Methods

Patients participating in this study were those with chronic ventricular ectopic beats suppressed by encainide during participation in short-term drug efficacy protocols.[2,3] Each

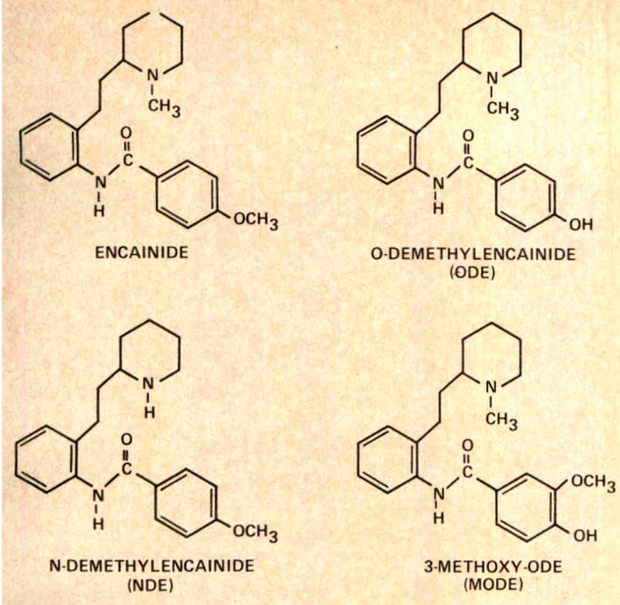

FIGURE 1. Chemical structure of encainide and 3 of its known metabolites in man.

TABLE I Clinical Characteristics and Drug Dose

Patient	Age (yr) & Sex	Cardiac Diagnosis	Total Daily Encainide Dose	Dose and Dose Interval
1	76M	Coronary HD	200	50 q6h
2	60M	Coronary HD	100	25 q6h
3	62F	Chest pain	70(105)*	35 q12h (35 q8h)*
4	60M	Cardiomyopathy†	200(150)‡	50 q6h (37.5 q6h)‡
5	48M	Coronary HD	140	35 q6h
6	71M	Coronary HD	100	25 q6h
7	49F	Presyncope	150	50 q8h
8	61M	Cardiomyopathy†	250	62.5 q6h
9	43M	Normal heart	200	50 q6h
10	42M	Cardiomyopathy†	160(80)§	40 q6h (20 q6h)§
11	54M	Coronary HD	200	50 q6h
12	65M	Coronary HD	140	35 q6h
13	59M	Coronary HD	187.5	62.5 q8h
14	65M	Coronary HD	210	70 q8h
Mean	58 ±10	... ...	165 ±51	... ...

* Dose increase at 4 months.
† Dilated (congestive) cardiomyopathy.
‡ Dose decrease at 6 months.
§ Dose decreased.
HD = heart disease; q6h and q8h = every 6 or 8 hours, respectively.

patient had undergone 1 or more 24-hour ambulatory electrocardiographic recording while receiving either no antiarrhythmic drugs or a placebo. The last 24-hour recording performed without antiarrhythmic drugs or with placebo before beginning long-term maintenance therapy with encainide was taken as the baseline recording. In some patients, slight dose adjustments were carried out during the first few weeks of chronic encainide therapy and patients were seen as outpatients after 1 to 2 weeks and 1 month of therapy. After 2 and 4 months of chronic encainide therapy, patients returned to the outpatient clinic for a clinical evaluation, 12-lead electrocardiogram, and 24-hour ambulatory electrocardiographic recordings. After approximately 6 months of therapy, each subject was admitted to the hospital for 3 days and underwent continuous telemetry monitoring on a cardiac floor. On Day 1, each patient contined to take his or her daily maintenance dose of encainide and underwent a 24-hour ambulatory electrocardiographic recording. On Day 2, each patient took the last dose of encainide and a 24-hour ambulatory electrocardiogram was obtained. Blood samples were drawn with use of a heparin lock 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after the last dose and stored in a glass test tube with a screw-on cap. Blood samples were spun and plasma was frozen for subsequent analysis. On Day 3, patients remained without encainide and a third 24-hour ambulatory electrocardiographic recording was performed. If the patient's arrhythmias returned, he or she was discharged with the same dose of encainide taken previously. Patients were seen in the outpatient clinic at 8 and 10 months and underwent clinical evaluation, 12-lead electrocardiogram, and 24-hour ambulatory electrocardiographic recordings. Patients were again hospitalized for 3 days after approximately 12 months of encainide therapy, and each underwent a drug withdrawal protocol similar to that performed at 6 months. Periodic laboratory safety data and ophthalmologic examinations were obtained in all patients.

Data analysis: Plasma from the 24-hour washout at 6 and 12 months was analyzed for drug concentration using a high pressure liquid chromatographic assay[7,10] which can measure unchanged encainide, ODE, MODE, and N-demethylencainide (NDE). Graphical plots of the log of the plasma concentration of encainide and each of its metabolites over time were made for each patient. Mean steady state plasma concentrations over a dose interval were calculated from the initial 6 to 8 hours of data after the final dose and a half-life was calculated from the least squares fit of the log-linear terminal portion of the log plasma concentration versus time curves.

Ambulatory electrocardiographic recordings were analyzed using the Stanford computer analysis system.[11] This provides accurate counts of total number of PVCs in each minute which were tabulated as PVCs per 15 minutes, hourly PVC count, and daily 24-hour totals. In addition, the total number of pairs and runs of ventricular ectopic beats were tabulated and verified by operator evaluation. Recordings of <24 hours' duration had the total PVC counts adjusted to reflect the shortened recording duration. The percent reductions in total ventricular ectopic beat counts at 2, 4, 6, 8, 10, and 12 months were compared with the initial baseline control recording.

For the 6- and 12-month drug withdrawals, graphical displays of PVC frequency over the 72-hour hospitalization were recorded. This included the initial 24 hours with maintenance encainide therapy and 48 hours after the final drug dose was administered. These graphs were inspected to assess the time of arrhythmia return. At the time corresponding to the return of arrhythmias, the plasma concentration of encainide and each of its metabolites was determined from the plots of drug and metabolite plasma concentration versus time. All data are reported as mean ± standard deviation.

Results

Patient population: Fourteen patients (12 men and 2 women) took part in the study. Their clinical characteristics are summarized in Table I. Two patients did not complete the 1-year trial. One patient (Patient 6) was withdrawn from the study after the 6-month drug withdrawal when it became apparent that his arrhythmias were actually supraventricular with aberration

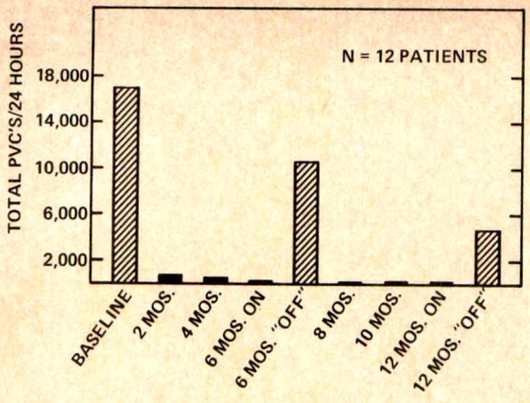

FIGURE 2. Average number of PVCs per 24 hours recorded on ambulatory electrocardiographic recordings for the 12 patients completing 1 year of encainide therapy. The crosshatched recordings done at baseline, 6 months, and 12 months were performed while the patient was not receiving ("off") encainide. However, because of the persistently high levels of encainide metabolites from 24 to 48 hours after the last dose of encainide, it is likely that the 6- and 12-month "off" encainide recordings were performed at a time when there was some persistent drug effect. This may account for the decreased number of PVCs compared with the baseline recording. The other recordings (**solid bars**) were all performed with the patient taking encainide; >95% average PVC reduction was seen on each of these recordings.

rather than ventricular in origin. The other patient (Patient 10) was withdrawn after several months of therapy because of failure to control his arrhythmias, probably due to progression of his cardiac disease (see later under Adverse Effects).

Encainide dose: The average encainide dosage was 165 ± 51 mg/day (range 100 to 250). This dosage was generally divided into 3 or 4 daily doses. Three patients underwent dosage adjustments during the 1-year period. Patient 3 had the dosage increased from 35 mg every 12 hours to 35 mg every 8 hours after approximately 4 months because she noted a return of palpitations toward the end of the dosage interval with the lower dose. Patient 4 had the dosage decreased from 50 to 37.5 mg every 6 hours because of excessive aberrant conduction of his atrial fibrillation during exercise treadmill testing. Patient 10 underwent a gradual reduction in dosage from 40 mg every 6 hours to 20 mg every 6 hours because of drug-induced sinus bradycardia with sinus pauses.

Antiarrhythmic effects: The total number of ventricular ectopic beats recorded in the baseline ambulatory electrocardiographic recordings as well as those obtained with drug therapy at 2, 4, 6, 8, 10, and 12 months are shown in Table II. The average baseline ventricular ectopic beat frequency was 17,021 ± 12,454/24 hours. Each of the ambulatory electrocardiographic recordings done with encainide revealed a marked reduction or total elimination of ventricular ectopic beats (Fig. 2). This reduction averaged well above 95% compared with the baseline value. Both the 6- and 12-month drug withdrawal recordings made from 24 and 48 hours after drug was discontinued showed a return of ventricular arrhythmias. Although the average number of ventricular ectopic beats in 24 hours was considerably higher during the drug withdrawal period than in each of the drug treatment periods, the 6-month withdrawal value of 10,469 ± 11,368 and the 12-month withdrawal value of 4,491 ± 5,340 were both below the baseline value.

Just as there was a marked reduction or total suppression of ventricular ectopic beats, there was nearly complete suppression of ventricular pairs (Table III) and ventricular salvos (Table IV). There was a distinct increase in the number of pairs and salvos at the 6- and 12-month withdrawal period, but neither returned completely to the baseline levels.

Adverse effects: Although only 2 patients were entirely free of adverse effects, in most patients the adverse effects occurred only infrequently or were of a minor nature; usually, they did not interfere with treatment. Eight patients had transient visual symptoms often described as a blurring of vision or difficulty with peripheral vision or both. Seven patients had transient lightheadedness or dizziness. Three had other central nervous system adverse effects, including intermittent tremor in 2 and a persistent facial numbness

TABLE II Total 24-Hour Premature Ventricular Contraction Count

Patient	Baseline	2 Months	4 Months	6 Months	24–48 Hours After Last Dose: 6 Months	8 Months	10 Months	12 Months	24–48 Hours After Last Dose: 12 Months
1	17,592	1,021	1,075	1,884	12,785	—	665	56	11,600
2	10,272	—	4	12	28	2	19	26	31
3	42,851	22	2	0	20,461	0	0	114	425
4	9,059	—	64	86	3,118	38	431	164	7,300
5	19,176	—	37	83	6,247	10	5	0	1,335
7	35,728	0	0	0	6,187	0	1	0	16,808
8	22,420	1,022	360	174	40,943	236	0	0	58
9	23,520	2,174	1,761	195	9,605	—	741	190	1,057
11	8,579	117	378	143	4,628	738	131	1,066	7,117
12	4,842	21	41	304	15,880	28	72	21	4,685
13	5,036	213	15	0	753	101	—	70	392
14	5,172	528	320	445	4,988	320	353	965	3,090
Mean	17,021 ±12,454	568 ±728	390 ±644	277 ±524	10,469 ±11,368	147 ±235	219 ±282	223 ±376	4,491 ±5,340

— = no data.

TABLE III Total Number of Ventricular Pairs in 24 Hours

Patient	Baseline	2 Months	4 Months	6 Months	24–48 Hours After Last Dose: 6 Months	8 Months	10 Months	12 Months	24–48 Hours After Last Dose: 12 Months
1	2,379	0	5	3	973	—	9	2	440
2	209	—	0	0	1	0	0	0	0
3	2,284	0	0	0	0	0	0	0	1
4	291	—	8	2	32	0	2	0	108
5	29	0	0	0	0	0	0	0	0
7	1,060	0	0	0	1	0	0	0	302
8	1,758	1	0	0	4,577	0	0	0	0
9	299	1	0	0	3,229	—	0	0	0
11	571	1	0	0	26	2	0	0	55
12	5	0	0	0	85	0	1	0	47
13	643	0	41	0	6	0	—	0	6
14	238	6	3	0	229	2	1	9	210
Mean	814 ±861	0.90 ±1.9	4.8 ±11.7	0.41 ±1.0	763 ±1,519	0.44 ±0.88	1.2 ±2.7	0.9 ±2.6	97 ±145

— = no data.

TABLE IV Total Number of Ventricular Salvos in 24 Hours

Patient	Baseline	2 Months	4 Months	6 Months	24–48 Hours After Last Dose: 6 Months	8 Months	10 Months	12 Months	24–48 Hours After Last Dose: 12 Months
1	151	0	0	0	201	—	0	0	45
2	0	—	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0
4	24	—	5	0	0	0	0	1	5
5	0	0	0	0	0	0	0	0	0
7	1,404	0	0	0	0	0	0	0	6
8	6	0	0	0	2	0	0	0	0
9	5	0	0	0	0	—	0	0	0
11	39	0	0	0	0	0	0	0	7
12	1	0	0	0	0	0	0	0	1
13	79	0	0	0	3	0	—	0	1
14	21	0	2	0	14	0	0	0	7
Mean	144 ±399	0	0.5 ±1.4	0	18 ±58	0	0	0.07 ±0.27	6 ±12

— = no data.

in 1. Three patients noted a bad taste in the mouth and 2 had gastrointestinal symptoms. One patient (Patient 10) had a drug-induced exacerbation of sinus bradycardia and sinus pauses with higher encainide doses. Reduction in the encainide dose in this patient resulted in a return of ventricular arrhythmias. The patient was treated with a permanent pacemaker for his sinus pauses, but despite continuation of encainide therapy had recurrences of sustained ventricular tachycardia and progression of congestive heart failure. This patient was withdrawn from encainide and ultimately underwent cardiac transplantation. Two patients, both with a history of presyncope before encainide administration, had single isolated episodes of syncope while taking encainide. In each instance, the drug was continued in its previous dose when electrocardiographic monitoring showed no explanation for the syncopal episode.

Plasma drug concentrations: A detailed reporting of the pharmacokinetics of encainide and its metabolites in these patients is beyond the scope of this report and will be presented in detail elsewhere.[12] However, in order to understand the relation between drug levels and antiarrhythmic effect, a brief summary is necessary. All but 1 of the patients showed the same pattern of encainide and encainide metabolite plasma concentrations. Encainide levels peaked very early after the final dose and had a rapid decrease with an average half-life of 1.10 ± 0.56 hours at 6 months and 1.05 ± 0.49 hours at 12 months. Two major metabolites, ODE and MODE, were identified in the plasma of these patients. Over a dose interval at steady state, the average plasma concentration of MODE and ODE greatly exceeded those of encainide itself (Fig. 3 and 4). Over a dose interval, the ratio of the mean plasma concentration of MODE to encainide was 5.02 ± 2.61 and the ratio of ODE to encainide was 5.15 ± 4.13 at 6 months. The ratios were similar at 12 months. Each of these metabolites had a much slower decline in plasma concentration than did encainide. The average half-life* of ODE was 11.1 ± 10.2 hours at 6 months and 10.9 ± 5.7 hours at 12

* True estimation of half-life cannot be determined because the continuing formation of metabolites from encainide may have been occurring. Such a determination requires direct administration of the metabolites.

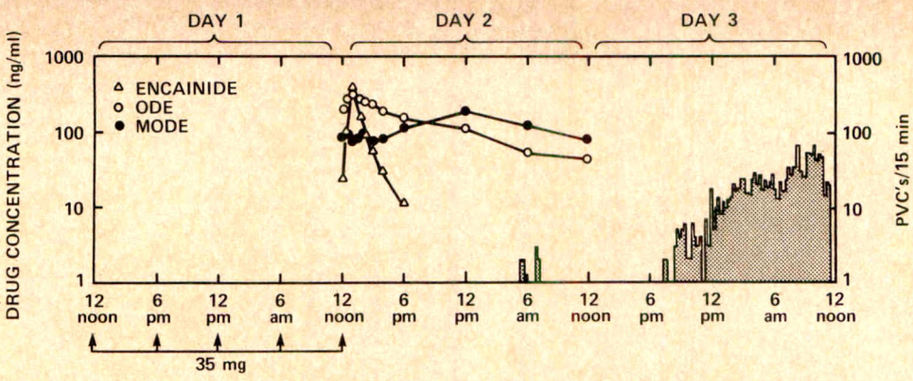

FIGURE 3. Data obtained from the 12-month withdrawal in Patient 5. Shown are the number of PVCs per 15 minutes obtained from ambulatory electrocardiographic recordings done during the 3-day withdrawal. On Day 1 the patient took 35 mg encainide every 6 hours, on Day 2 no encainide was given and blood was sampled throughout the 24-hour period, and on Day 3 the patient remained off encainide. In this patient, encainide plasma concentration (**open triangles**) peaked early and were undetectable by 6 hours after the final dose of encainide. The plasma concentration of O-demethylencainide (ODE) and 3-methoxy-O-demethylencainide (MODE) remained high throughout the 24-hour period. Although a few PVCs occurred at 6 A.M. on Day 2 (18 hours after the last dose of encainide), they do not return consistently until 32 to 38 hours after the last dose of encainide. This patient's reaction was the most striking example suggesting that antiarrhythmic effect was due to encainide's metabolites.

months. MODE was present in higher plasma concentrations and decayed even more slowly than did ODE. In fact, some patients had almost no decrease of MODE over the 24-hour washout period.

One patient (Patient 4) had a different pattern of metabolism. This patient had higher levels of and a longer half-life for encainide (3.3 hours at 6 months and 2.5 hours at 12 months) than other patients and had levels of ODE which exceeded those of MODE. Furthermore, a third metabolite, NDE, was also detected in low plasma concentrations in this patient.

Return of arrhythmias after drug withdrawal: relation to drug plasma concentration: There were a total of 24 drug withdrawals in the 12 patients completing 1 year of treatment with encainide. Eleven of these withdrawals were not suitable for evaluating the relation between arrhythmia return and encainide and encainide metabolite plasma concentration. In 2 instances the 6-month withdrawal plasma samples were not analyzed using the high pressure liquid chromatographic assay. After 4 drug withdrawals, there was no return of ventricular arrhythmias during the 48-hour washout period. In several of these instances, patients were discharged not receiving encainide, and ambulatory electrocardiographic recordings done after discharge documented a return of ventricular arrhythmias. In 5 drug withdrawals, ventricular arrhythmias definitely returned but they did so gradually and it was difficult to determine a specific time at which the arrhythmias returned. Excluding these 11 withdrawals left 13 drug withdrawal periods in which the time of return of ventricular arrhythmias was well-defined and the plasma concentrations of encainide and its metabolites were available.

After encainide withdrawal, the time of arrhythmia return ranged from approximately 6 to approximately 38 hours (median 12 to 14). In 9 of the 13 withdrawals, ventricular arrhythmias returned from 2.5 to 28 (median 8) hours *after* encainide was no longer detectable in the plasma (Fig. 3 and 4). In 2 instances ventricular ar-

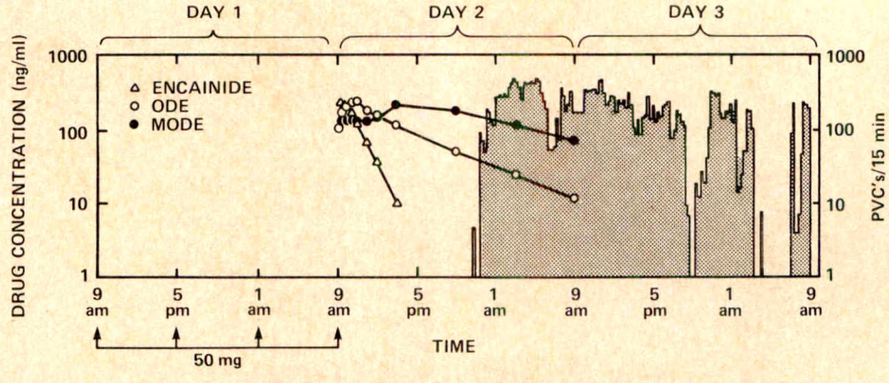

FIGURE 4. Data obtained from encainide withdrawal at 12 months in Patient 7. Premature ventricular contractions did not return until 14¼ hours after the last dose of encainide. At the time of PVC return, the ODE plasma concentration was 42 ng/ml and the MODE plasma concentration was 180 ng/ml. The last detectable encainide level occurred 6 hours after the last dose of encainide was taken, a full 8 hours before the return of PVCs.

rhythmias returned at 6 and 11 hours, which was approximately the same time as encainide decayed to undetectable levels. In only 2 drug withdrawals were there measurable encainide levels persisting beyond the time of ventricular arrhythmia return. These 2 withdrawals were both in Patient 4 who also had the unusual pattern of encainide metabolism. Excluding this patient, the average plasma concentrations of ODE and MODE at the time of ventricular arrhythmia return were 71.7 ± 49 ng/ml (range 15 to 140) and 172 ± 74 ng/ml (range 78 to 320).

Discussion

Patients entering this study were known to have had ventricular arrhythmias suppressed by short courses of oral encainide therapy. Several previous publications have indicated the drug causes nearly total ventricular ectopic beat suppression during short-term administration.[1–4] Our study documents ongoing antiarrhythmic effect over a 1-year period in a group of subjects with complex ventricular ectopic beats. The initial short-term excellent antiarrhythmic response was maintained in these subjects and ventricular ectopic beat suppression averaged well over 95% throughout the year of treatment. Perhaps more importantly the suppression of pairs and salvos was also nearly complete. These observations suggest that encainide might be an excellent antiarrhythmic agent to use in clinical trials designed to test the hypothesis that ventricular ectopic beat suppression can prevent sudden cardiac death in high-risk subgroups.

Although most subjects in this study experienced adverse effects, they were generally minor and well-tolerated. Dizziness or lightheadedness and visual disturbances were the most common adverse effects. One patient experienced dose-related worsening of bradyarrhythmias and long sinus pauses. Although in our overall experience with encainide this has been an uncommon adverse effect, it does indicate the drug has the potential to cause de novo or aggravate preexisting sinus nodal dysfunction. The same patient with the sinus pauses also had several recurrences of sustained ventricular tachycardia. While we cannot entirely exclude the possibility of encainide exacerbation of ventricular irritability,[13] overall, it seems most probable that these episodes represented a failure of the drug to control ventricular tachycardia in a patient with a progressive cardiomyopathy.

The most important finding of this study was the observation that 1 or both of the encainide metabolites, MODE and ODE, may have been contributing to the drug's antiarrhythmic activity during long-term oral therapy. During long-term oral dosing these metabolites are present in plasma concentrations which greatly exceed those of encainide itself. Because of their high plasma concentrations relative to encainide's and their considerably longer half-lives during drug withdrawal, antiarrhythmic activity persisted well beyond the time when encainide plasma concentrations become unmeasurable. Arrhythmias returned at a time when considerable plasma levels of both metabolites were present in all patients. While this evidence strongly suggests that these metabolites account for a portion of encainide's antiarrhythmic activity, the evidence is only circumstantial. We cannot determine whether this pharmacologic activity results from 1 or both of these metabolites. Nor can we entirely exclude either the possibility that encainide in extremely low and unmeasurable (using the high pressure liquid chromatographic technique) plasma concentrations or the persistence of high encainide tissue concentrations are accounting for the antiarrhythmic activity seen. Further unraveling of these points will require direct administration of MODE and ODE to patients with arrhythmias.

The finding that metabolites may account for a portion of encainide's antiarrhythmic activity has several implications for therapy with this drug. It is clear that measurement of encainide plasma concentrations alone may bear little relation to drug effect. In order for measurement of plasma drug levels to be of value, it will be necessary to learn a great deal more about the relative potency of the various metabolites and the contribution of each to antiarrhythmic action as well as adverse effects. The extremely slow decay of plasma concentration of MODE and ODE and the finding that these compounds have antiarrhythmic activity explain the fact that pharmacologic effect for encainide may persist well beyond the time when encainide itself is no longer detectable in the plasma. Furthermore, the different pattern of encainide levels and metabolite formation in 1 of our patients suggests intersubject variation may further complicate the situation. Roden et al[1] also noted intersubject variation in pattern of metabolism of encainide since 1 of 11 patients in their series did not form ODE.

Previous studies indicated that encainide had a short half-life averaging approximately 2 to 3 hours. Thus, the present study was designed with a 24-hour washout during which bloods would be obtained for drug plasma concentration. It was anticipated that encainide would be gone from the plasma by the end of 24 hours in virtually all patients; thus, the ambulatory electrocardiographic recording obtained 24 to 48 hours after the last dose of encainide would be adequate for use as a drug withdrawal ambulatory electrocardiographic recording to document the return of arrhythmias. This policy followed the usual rule of having discontinued the drug for at least 5 half-lives before making a "drug-free" recording. Although many patients had a return of arrhythmias by 24 hours after the last dose of encainide, a number of patients did not. The high level of encainide metabolites present suggests that the failure of arrhythmias to return during this time may have been due to the metabolites' presence. This may be the explanation for the fact that the 6- and 12-month withdrawals did not show a complete return of arrhythmias to baseline levels.

The presence of pharmacologically active metabolites with slow plasma decay suggests that these metabolites do not reach steady-state for several days or longer after initiation of oral maintenance encainide doses. Since these metabolites may potentially account for some of encainide's toxicity as well as its efficacy, it seems im-

portant to allow several days or more to elapse with any given maintenance dose before going to a higher dose. Further observations with regard to the accumulation of these metabolites will be necessary in order to determine when they reach steady-state plasma concentration.

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Beat-to-Beat Left Ventricular Performance in Atrial Fibrillation: Radionuclide Assessment With The Computerized Nuclear Probe

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There is wide beat-to-beat variability in cycle length and left ventricular performance in patients with atrial fibrillation. In this study, left ventricular ejection fraction and relative left ventricular volumes were evaluated on a beat-to-beat basis with the computerized nuclear probe, an instrument with sufficiently high sensitivity to allow continuous evaluation of the radionuclide time-activity curve. Of 18 patients with atrial fibrillation, 5 had mitral stenosis, 6 had mitral regurgitation, and 7 had coronary artery disease. Fifty consecutive beats were analyzed in each patient. The mean left ventricular ejection fraction ranged from 17 to 51%. There was substantial beat-to-beat variation in cycle length and left ventricular ejection fraction in all patients, including those with marked left ventricular dysfunction. In 14 patients who also underwent multiple gated cardiac blood pool imaging, there was an excellent correlation between mean ejection fraction derived from the nuclear probe and gated ejection fraction obtained by gamma camera imaging ($r = 0.90$). Based on beat-to-beat analysis, left ventricular function was dependent on relative end-diastolic volume and multiple preceding cycle lengths, but not preceding end-systolic volumes. This study demonstrates that a single value for left ventricular ejection fraction does not adequately characterize left ventricular function in patients with atrial fibrillation. Furthermore, both the mean beat-to-beat and the gated ejection fraction may underestimate left ventricular performance at rest in such patients.

Atrial fibrillation is characterized by an irregularly irregular ventricular response resulting in marked variations in beat-to-beat left ventricular function. Although several studies have evaluated the determinants of beat-to-beat left ventricular performance in this arrhythmia, these studies have been limited partially by methodologic constraints.[1–8] They generally have not allowed direct assessment of left ventricular function in a sufficiently large number of consecutive beats in each patient. In addition, analyses have been based predominantly on data pooled from numerous patients and often have involved derived indirect indexes of left ventricular performance. These studies also have not addressed the potential differences in analysis due to different underlying disease states or the degree of basal left ventricular dysfunction.

In clinical practice, global left ventricular ejection fraction usually is obtained from contrast ventriculography by analysis of a single beat, or at most from 3 to 5 beats, even in patients with atrial fibrillation. With use of multigated equilibrium radionuclide angiocardiography, left ventricular ejection fraction is calculated from the summation of several hundred individual cardiac cycles. Because of the marked beat-to-beat variation, the applicability of these approaches to patients with atrial fibrillation has been questioned. In the present study, left ventricular ejection fraction was evaluated with the computerized nuclear probe, an instrument with sufficiently high sensitivity to allow beat-to-beat assessment of the radionuclide time-ac-

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TABLE I Distribution of Beat-to-Beat Cycle Length and Ejection Fractions in Patients With Atrial Fibrillation

Case	Diagnosis	Group	Cycle Length (s)*	Probe LVEF (%)*	Outliers (n out of 50)*,†
1	MS	I	0.86 ± 0.30	49 ± 13	20
2	MS	I	0.86 ± 0.30	49 ± 9	7
3	MS/AR	I	0.87 ± 0.26	47 ± 11	10
4	MS	I	1.10 ± 0.63	46 ± 16	24
5	MS/AR	I	1.10 ± 0.45	42 ± 9	12
6	MR/TR	II	0.98 ± 0.37	38 ± 19	29
7	MR	II	0.61 ± 0.30	18 ± 16	25
8	MR	II	0.90 ± 0.43	42 ± 18	27
9	MR	II	1.16 ± 0.72	50 ± 15	28
10	MR	II	0.92 ± 0.26	40 ± 10	9
11	MR/TR	II	0.60 ± 0.14	47 ± 11	9
12	CAD	III	0.85 ± 0.43	47 ± 15	27
13	CAD	III	0.87 ± 0.33	47 ± 11	12
14	CAD	III	0.63 ± 0.34	32 ± 15	19
15	CAD	III	0.83 ± 0.39	17 ± 12	14
16	CAD	III	0.79 ± 0.35	34 ± 18	33
17	CAD	III	1.10 ± 0.82	26 ± 17	21
18	CAD	III	0.69 ± 0.18	45 ± 14	19

* Mean ± 2 standard deviations of beat-to-beat data (n = 50 beats).
† Based on left ventricular ejection fraction, number of beats falling outside the range derived from the mean ± the expected variability.
AR = aortic regurgitation; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MS = mitral stenosis; TR = tricuspid regurgitation.

tivity curve.[9–11] With use of a multichannel strip chart recorder, the left ventricular volume curve can be displayed in synchrony with the electrocardiogram. This allows calculation of beat-to-beat left ventricular ejection fraction and relative left ventricular volumes, which can be related directly to cycle lengths. This approach has been used in this laboratory, as well as by other investigators,[9,11,12] to assess the left ventricular functional responses to atrial and ventricular premature beats.

The goals of this study were (1) to determine the beat-to-beat variability of left ventricular ejection fraction in atrial fibrillation and relate individual beat measurements to mean values obtained by averaging multiple beats, and (2) to use this beat-to-beat analysis to evaluate some of the potential control mechanisms operative in atrial fibrillation. From a clinical perspective, this analysis should provide relevant insights concerning the utility of the ejection fraction measurement in atrial fibrillation.

Methods

Patient group: Eighteen patients with atrial fibrillation were studied. Three additional patients were excluded because of excessive respiratory motion or concomitant premature ventricular beats, or both. In all cases, patients had a stable rhythm of atrial fibrillation for at least 3 months before the study. The mean age was 67 years (range of 53 to 90). Twelve patients were men and 6 women. The primary etiologic diagnosis was determined with clinical evaluation and both M-mode and 2-dimensional echocardiography in all patients (Table I). Cardiac catheterization data also were available in 5 patients. Patients were classified into 3 groups on the basis of the primary diagnosis: (1) mitral stenosis (5 patients), (2) mitral regurgitation (6 patients), and (3) coronary artery disease (7 patients). In group 3, all 7 patients had previous myocardial infarction; none were unstable at the time of the study or had any clinical evidence of associated mitral regurgitation. The mean heart rate determined over approximately 1 minute in each patient was 69 beats/min with a range of 52 to 100 beats/min. All patients were receiving digitalis for control of ventricular response. Thus, only patients with relatively slow heart rates were studied. Three patients had a history of congestive heart failure and were taking diuretic drugs. No patient was receiving calcium slow channel antagonists.

Patient protocol: All patients were studied with the computerized nuclear probe (Bios, Valhalla, New York) in the supine position after technetium-99m in vivo blood pool labeling (25 mCi). The nuclear probe was positioned over the left ventricular and background regions of interest using algorithms and operator routines previously described.[9] Patients breathed shallowly during data acquisition. The analog output from the nuclear probe was interfaced with a multichannel strip chart recorder (Elema-Schonander Mingograph 34, Solna, Sweden). This allowed continuous display and permanent recording of a simultaneously acquired left ventricular time-activity curve, background activity level, and electrocardiographic signal (Fig. 1). After final probe positioning and confirmation of patient stability, beat-to-beat data were acquired for approximately 1 minute; 50 consecutive beats then were identified for subsequent analysis. As previously described, relative end-diastolic, end-systolic, and stroke volumes and ejection fraction were calculated manually for each beat.[9] Each beat was measured twice and the mean used for analysis.

There are potential problems with the use of radionuclide techniques for assessment of left ventricular performance in atrial fibrillation. In patients with an enlarged left atrium, left atrial radioactivity may contribute to the left ventricular time-activity curve and may artifactually decrease the calculated left ventricular ejection fraction. However, with the probe, particular care was taken to assure adequate caudal tilt, minimizing left atrial-left ventricular overlap. In addition, determination of the optimal left ventricular and background positions with the computer-derived algorithms is more difficult in patients with marked beat-to-beat fluctuations in stroke volume. This occurs because the positioning algorithms are based on beat-to-beat changes in stroke counts and average counts.[9–11] Particular care was taken to move the probe slowly allowing the algorithms to average more beats in each position. This technique also has been used successfully to study the effects of atrial and ventricular premature beats.[11,12]

In 14 patients, multiple gated equilibrium cardiac blood pool imaging was performed within 30 minutes of the initial

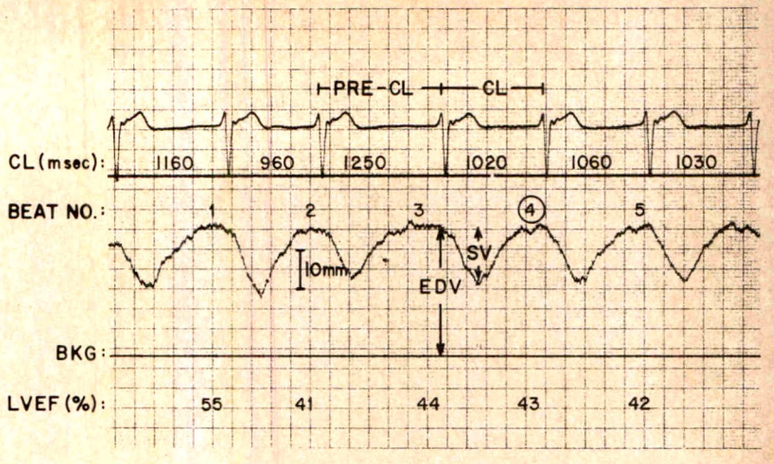

FIGURE 1. Actual beat-to-beat data obtained with the computerized nuclear probe. The data are displayed on the stripchart recording showing the electrocardiogram, the radionuclide time-activity curve, and the background (BKG) activity level. Beat-to-beat values for cycle length (CL) and ejection fraction are shown for 5 consecutive beats. Beat 4 is the beat in question (**circled**). The immediately preceding cycle length is 1,020 ms, whereas the second preceding cycle length is 1,250 ms. Stroke volume (SV) and end-diastolic volume (EDV) are derived directly from the stripchart recording. LVEF = left ventricular ejection fraction.

nuclear probe study.[13] Data were acquired in the left anterior oblique position providing the optimal separation of right and left ventricles and with 10° to 15° caudal tilt. Data were acquired for 8 to 10 minutes with a portable gamma camera and minicomputer (Technicare VIP 450, Solon, Ohio). All beats were accepted; there was no rejection of beats with excessively long- or short cycle lengths. Left ventricular ejection fraction was calculated using a variable region of interest and quadrant threshold edge definition (Q-MICA program). The remaining 4 patients did not undergo multiple gated blood pool imaging for logistic reasons.

Statistical analysis: Group data are presented as the mean ±1 standard deviation, unless otherwise indicated. Comparisons within individual patients were made by the paired *t* test. Linear (univariate and multivariate), polynomial, and exponential regression equations and correlation coefficients were determined with use of standard formulas. Only significant ($p < 0.05$) correlation coefficients are included in the tables.

In the manual analysis of each probe study, the mean and standard deviation of the 50 consecutive beats were determined for stroke counts (measured in millimeters), end-diastolic counts (millimeters), end-systolic counts (millimeters), and left ventricular ejection fraction (stroke counts divided by end-diastolic counts × 100) (Fig. 1). The mean value for ejection fraction in the 50 beats was used for comparisons with multigated blood pool studies.

On the basis of our previously published data, the absolute variability of beat-to-beat left ventricular ejection fraction measurements was ±5.8% (expressed as ±2 standard deviations in ejection fraction units).[9] These data were derived from 10 beats each in 71 patients with normal sinus rhythm. There was no significant difference in patients with normal and abnormal mean ejection fractions. In each patient in the present study, the mean ejection fraction ±6% was calculated; this range then defined the expected intrinsic variability for a given patient assuming sinus rhythm. Individual beats with ejection fractions that fell outside this range were considered to be significant outliers.

Correlation coefficients were derived based on the 50 consecutive beats in each patient. Beat-to-beat data for the overall group of 18 patients were not pooled. Left ventricular performance (both ejection fraction and relative stroke volume) was related to cycle length by a linear regression equation, an exponential regression equation, and up to a fourth order polynomial regression equation. In all instances, the linear regression equation resulted in the highest consistent correlation coefficient. Therefore, all subsequent analyses only involved the linear equations. Stepwise multiple linear regression equations then were obtained relating left ventricular performance to both the cycle length immediately preceding the beat in question and the second preceding cycle length, that is, 2 beats before the beat in question.[14] This allowed determination of the effects of abrupt alterations in cycle length on ventricular function. This approach also has been used in previous studies of atrial fibrillation.[5–7] The potential role of end-systolic volume in addition to preceding cycle lengths also was assessed by stepwise multiple linear regression analysis.

Results

In the overall group of 18 patients with atrial fibrillation, the mean left ventricular ejection fraction obtained with the probe ranged from 17 to 51% (Table I). The mean (±1 standard deviation) left ventricular ejection fraction in the 3 patient subgroups averaged as follows: (1) mitral stenosis (47 ± 3%, n = 5); (2) mitral regurgitation (39 ± 11%, n = 6); and (3) coronary artery disease (35 ± 12%, n = 7). Six patients had markedly abnormal left ventricular performance (mean left ventricular ejection fractions less than 40%): 2 with mitral regurgitation and 4 with coronary artery disease.

There was substantial beat-to-beat variation in cycle length and left ventricular ejection fraction in all patients. For the overall group of 18 patients, the pooled standard deviation of beat-to-beat ejection fraction based on a total of 900 individual cardiac cycles was 6.9%, which is more than twice the value for normal sinus rhythm (2.9%).[9] Thus, using ±2 standard deviations (accounting for 95% of variability), a mean ejection fraction value generally would be derived from individual beats with ejection fractions both greater and lesser by 14%. For example, a mean ejection fraction of 40% could be expected to be derived from beats as low as 26% and as high as 54%. This was apparent in each disease subgroup, as well as in those with mean ejection fractions below 40% and those with ejection fractions between 40 and 51% (Fig. 2 and 3). On the basis of the analysis of 50 beats in each patient, 32 ± 7 individual cardiac cycles had ejection fractions within the range derived from the mean and expected variability. Of the beats falling outside this range, there was an equal distribution above and below the outer limits (9 ± 3

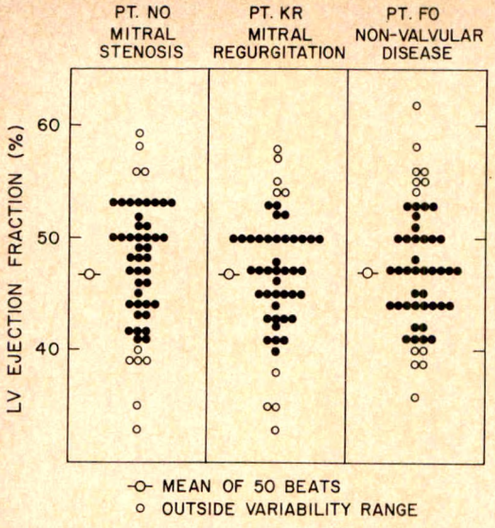

FIGURE 2. Beat-to-beat left ventricular (LV) ejection fraction in 3 patients with atrial fibrillation and mean ejection fraction of approximately 47%. Left ventricular ejection fraction is shown for 50 consecutive beats in each patient. The beats falling within the variability range (see text) are indicated by **closed circles.** The beats falling outside the variability range are shown as **open circles.** Note that in each disease state there is marked beat-to-beat variability in ejection fraction, with a substantial number of beats falling both above and below the limits of variability.

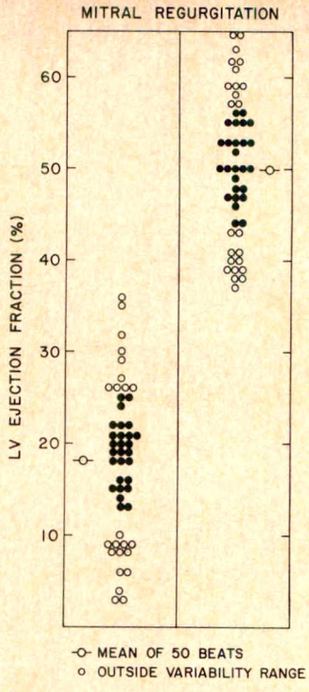

FIGURE 3. Beat-to-beat left ventricular ejection fraction in 2 patients with mitral regurgitation. One patient (**left panel**) had marked left ventricular dysfunction, whereas the other patient (**right panel**) had relatively preserved left ventricular (LV) performance. There is marked beat-to-beat variability in left ventricular ejection fraction in both patients. The format is the same as in Figure 2.

beats versus 10 ± 3 beats, p = not significant [NS]). In individual patients, 8 to 28% (mean 18%) of individual beats exceeded the variability range, whereas 6 to 32% (mean 19%) fell below the variability range (Table I). This beat-to-beat variation occurred independent of underlying disease (mitral valvular or coronary artery disease) and the level of baseline global left ventricular function. Specifically, there was no relation between the number of outliers and the mean ejection fraction (p = NS).

In the 14 patients who underwent both a nuclear probe study and multiple gated blood pool imaging, there was no significant difference in mean probe and gated camera ejection fractions (39 ± 11% versus 41 ± 10%, p = NS). The mean interstudy difference was 4 ± 1%. In no instance did the 2 values differ by more than 9%. There was excellent agreement between mean ejection fraction derived from the nuclear probe and gated ejection fraction obtained by gamma camera imaging (r = 0.90, p <0.001) (Fig. 4). This close relation may not persist at higher heart rates (>100 beats/min), when the systolic ejection time may vary substantially. Thus, the ejection fraction derived from the electrocardiographically gated summed time-activity curve is a relevant index of mean beat-to-beat ejection fraction in atrial fibrillation. However, there is substantial beat-to-beat variation, casting doubt on the clinical utility of analyses based only on 1 beat or a few beats.

By assessment of the dependence of left ventricular function on loading conditions, specifically end-diastolic volume and preceding cycle lengths, the relative roles of the Frank-Starling mechanism[15,16] and the interval-strength relations[17,18] were addressed (Table II). On a beat-by-beat basis, left ventricular ejection fraction correlated positively with cycle length in each patient (Frank-Starling effect) (Fig. 5). In patients with mitral stenosis (Group I), the correlation coefficient ranged

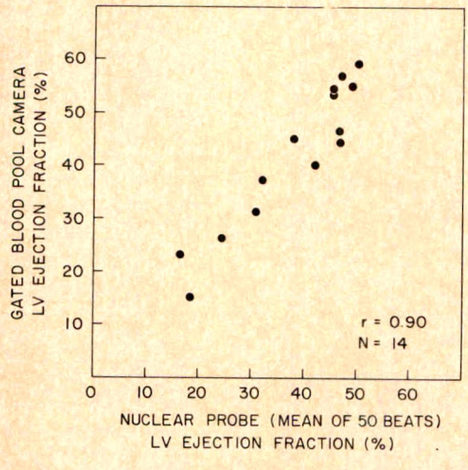

FIGURE 4. Left ventricular (LV) ejection fraction derived from gated blood pool imaging and from the mean of 50 beats obtained with the computerized nuclear probe. Note the excellent correlation between values derived from each technique. There is no systematic under- or overestimation with the probe (camera ejection fraction = 1.1 [probe ejection fraction] + 1.8).

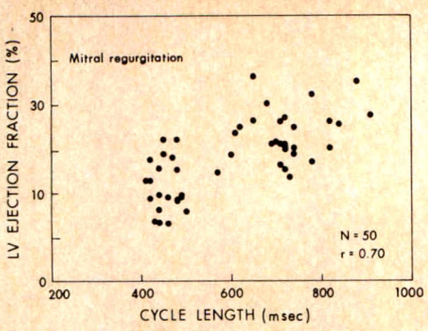

FIGURE 5. Dependence of left ventricular (LV) ejection fraction on cycle length in a patient with mitral regurgitation. Fifty consecutive beats were analyzed in this patient. Note the correlation between left ventricular ejection fraction and beat-to-beat cycle length.

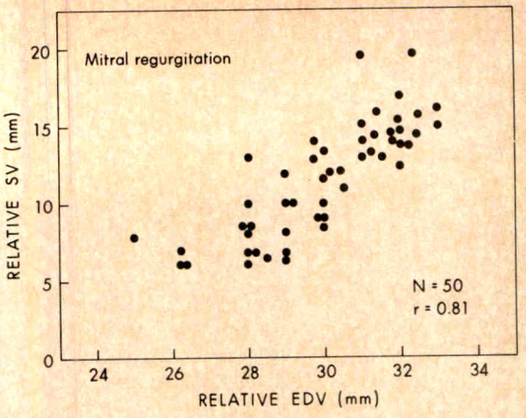

FIGURE 6. Dependence of relative stroke volume on relative end-diastolic volume (EDV) in a patient with mitral regurgitation. This is a demonstration of the Frank-Starling effect. Larger end-diastolic volumes are associated with larger stroke volumes (SV).

from 0.51 to 0.59. In patients with mitral regurgitation (Group II), the correlation coefficient ranged from 0.38 to 0.82. In patients with coronary disease (Group III), the correlation coefficient ranged from 0.50 to 0.81. By applying the multiple linear regression analysis, the additive effects of including the second preceding cycle length were assessed (Table II). This allowed evaluation of whether the intervals between preceding beats had direct effects on the left ventricular contractile state (interval-strength relation). All 6 patients with mitral regurgitation demonstrated significant multiple correlation coefficients when the second preceding cycle length was taken into account. The multiple correlation coefficients now ranged from 0.55 to 0.89. However, in each case, the added coefficient was negative; that is, there was a significant inverse relation between ejection fraction and the second preceding cycle length. In direct contrast, the added factor was not significant in any of the patients with mitral stenosis (Group I). There was a variable response in the patients with nonvalvular disease, with only 2 of 7 patients demonstrating significant multiple correlation coefficients. These 2 patients had the lowest ejection fractions (17 and 26%) in the group. Relative end-systolic volume in the preceding beats was not a significant factor in addition to preceding cycle lengths.

Stroke volume correlated significantly with immediately preceding cycle length in all patients and with end-diastolic volume in all except 1 patient with coronary artery disease and a low ejection fraction (11%) (Fig. 6). Once again, addition of the second preceding cycle length resulted in significantly improved correlation coefficients for all patients with mitral regurgitation but only 2 of 7 patients with coronary disease. None of the patients with mitral stenosis had significant interaction of the second preceding cycle length and global left ventricular performance (Table II).

TABLE II Linear Correlation Coefficients in Patients With Atrial Fibrillation Based on 50 Consecutive Beats

Case	Group	SV vs EDV	EDV vs CL	LVEF vs CL	LVEF vs CL+ PRE-CL*	SV vs CL	SV vs CL+ PRE-CL*
1	I	0.79	0.54	0.59	NS	0.62	NS
2	I	0.67	0.58	0.59	NS	0.71	NS
3	I	0.81	0.85	0.59	NS	0.76	NS
4	I	0.73	0.46	0.56	NS	0.63	NS
5	I	0.68	0.60	0.51	NS	0.65	NS
6	II	0.81	0.75	0.82	0.87	0.84	0.89
7	II	0.58	0.47	0.70	0.89	0.72	0.90
8	II	0.45	0.45	0.68	0.75	0.79	0.86
9	II	0.62	0.61	0.77	0.83	0.84	0.88
10	II	0.61	0.36	0.71	0.80	0.71	0.79
11	II	0.59	NS	0.38	0.55	0.36	0.55
12	III	0.75	0.67	0.71	NS	0.79	NS
13	III	0.84	0.77	0.72	NS	0.84	NS
14	III	0.65	0.52	0.64	0.73	0.68	0.75
15	III	0.41	0.36	0.81	NS	0.84	NS
16	III	0.75	0.71	0.75	0.78	0.82	0.85
17	III	NS	NS	0.74	NS	0.80	NS
18	III	0.73	0.50	0.67	NS	0.70	NS

* Stepwise multiple linear regression (NS = no significant additive term).
CL = cycle length; EDV = end-diastolic volume; LVEF = left ventricular ejection fraction; NS = not significant; PRE-CL = preceding cycle length; SV = stroke volume.

Discussion

This radionuclide study clearly demonstrates that no single value for left ventricular ejection fraction adequately characterizes left ventricular function in atrial fibrillation. In each patient, there was a substantial number of cardiac cycles in which left ventricular ejection fraction exceeded the mean value. The mean left ventricular ejection fraction may substantially underestimate beat-to-beat left ventricular function in the resting state—by as much as 14% in ejection fraction units using mean data. However, there was good agreement between average left ventricular fraction obtained by electrocardiographically gated equilibrium blood pool imaging and the mean of beat-to-beat function obtained with the nuclear probe; this agrees with a previous study in which a nonimaging probe was used.[19] All patients in this study were receiving digitalis, and this may have impact on our findings. The wide fluctuations in cycle length in atrial fibrillation may result in distortion of the gated time-activity curve. The major differences in the configuration of the left ventricular volume curve occur during diastole, with shortening of the mid to late diastolic phases. As heart rate increases, the duration of diastasis decreases and the configuration of the diastolic curve changes.

The present study evaluated the presence and role of the Frank-Starling mechanism[15,16] and the interval-strength relation[17,18,21] in determining beat-to-beat left ventricular performance in atrial fibrillation (Table II). The significant correlations between either ejection fraction or stroke volume and cycle length are consistent with the Frank-Starling mechanism. Thus, a longer cycle length (slower heart rate) results in a higher level of left ventricular performance. Furthermore, the significant correlation between stroke and end-diastolic volumes in all but 1 patient is further evidence for the Frank-Starling relation. This major dependence of ejection fraction on preload occurred in all 3 patient groups over a broad range of basal ejection fractions. This interaction also should occur in patients with normal sinus rhythm. The optimal characterization of this relation was derived using a linear regression analysis. Although a nonlinear phase has been shown experimentally,[16] neither a polynomial regression equation up to the fourth order nor a exponential equation resulted in a consistently better relation in these patients.

If the Frank-Starling mechanism were the only determinant of left ventricular performance in atrial fibrillation, then one would expect an extremely close relation between cycle length and ejection fraction in a given patient. However, significant correlation coefficients ranged from 0.38 to 0.82, with only 8 of 18 patients having correlation coefficients greater than 0.70. The direct role of changes in afterload could not be assessed in this study, because aortic pressure and systemic vascular resistance were not measured on a beat-to-beat basis. However, the interval-strength relation appeared to be operative in all patients with predominant mitral regurgitation. In each instance, linear regression analysis involving not only the cycle length but also the preceding cycle length resulted in a significantly improved correlation, although the dependent variables had opposing effects. This suggests that the systolic phase of left ventricular contraction is modulated by 2 independent processes in mitral regurgitation. The interval between preceding beats appears to have a direct effect on the contractile state of the left ventricle 2 beats later, causing a change in systolic force development. These findings agree in concept with those in previous studies.[4–7]

In contrast to mitral regurgitation, no patient with mitral stenosis had evidence of a significant interval-strength relation. Because a substantially smaller proportion of diastolic filling takes place in early diastole in mitral stenosis than in regurgitation, the duration of left ventricular filling may be of more importance in determining left ventricular function in mitral stenosis than in regurgitation. In this case, the Frank-Starling mechanism would appear to predominate. In coronary disease, the interval-strength relation only appears to be present in 2 patients with severe left ventricular dysfunction.

Previous studies of atrial fibrillation have employed a variety of techniques.[1–7] These analyses have been limited in that left ventricular ejection fraction and volumes could not be determined in an adequately large number of consecutive beats in each patient, including those with regional dyssynergy. These studies, as well as those in conscious instrumented baboons[15] have suggested that the Frank-Starling mechanism was the major determinant of left ventricular function. The data from the present study confirm these results and furthermore suggest that in patients with mitral regurgitation the interval-strength relation also plays an important role in determining left ventricular performance. Future studies with the nuclear probe will not be limited to ejection phase indexes of left ventricular function and volumes but will include a detailed assessment of diastolic function, as well as pressure-volume relations in atrial fibrillation.[22]

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Comparative Effects of Beta-Adrenergic Blocking Drugs On Experimental Ventricular Fibrillation Threshold

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Recent clinical studies suggest that certain beta-adrenergic blocking drugs, such as timolol, may reduce sudden death in patients with ischemic heart disease, but the mechanism has not been established. To assess and compare antifibrillatory effects of beta-blocking drugs as a potential mechanism of sudden death prevention, the ventricular fibrillation (VF) threshold was measured in anesthetized, open-chest dogs before and after 3 minutes of coronary ischemia during intravenous administration of saline solution or 3-fold serial increments (0.003 to 1.0 mg/kg) of 5 beta-blocking drugs with various accessory properties. Ventricular fibrillation occurred in control studies after delivery of a current train of 11.7 ± 7.6 mA in the nonischemic state and 7.0 ± 7.4 mA during ischemia (n = 46). All 5 beta-blocking drugs but not saline solution caused substantial (average 6-fold) increases ($p < 0.001$) in the VF threshold under both nonischemic (to 67 ± 30 mA) and ischemic conditions (to 42 ± 31 mA). The maximal VF thresholds attained were similar for individual drugs: timolol, 71, 39 mA (nonischemic, ischemic conditions, n = 10); pindolol, 81, 46 mA (n = 7); propranolol, 58, 36 mA (n = 7); metoprolol, 60, 40 mA (n = 7); and labetolol, 67, 52 mA (n = 6). The effective doses (mg/kg) at which maximal effects first occurred, however, varied widely: timolol, 0.01 mg/kg; pindolol, 0.1 mg/kg; propranolol, 0.3 mg/kg; metoprolol, 1.0 mg/kg; and labetolol, 1.0 mg/kg. The antifibrillatory potency (mg/kg) generally paralleled known ratios of beta-blocking efficacy, except for timolol's apparently greater potency. Interruption of stellate ganglionic impulses accounted for part of the augmentation in VF threshold. Thus, a substantial antifibrillatory effect accompanies experimental blockade of beta-adrenergic stimuli. An increase in VF threshold is suggested as a possible protective mechanism by which beta-blocking drugs reduce sudden death.

Sudden cardiac death has been termed the major challenge confronting contemporary cardiology.[1] Ventricular fibrillation (VF) occurring during usual daily activities in patients with underlying coronary artery disease is the precipitating cause in most patients.[1–4] Unfortunately, treatment with standard and also newer class I antiarrhythmic agents has not yet been shown effective.[4–8] The possibility that certain beta-adrenergic blocking agents (antiarrhythmic class II) might decrease cardiac death, particularly sudden cardiac death in postinfarction patients, was initially suggested by studies dating back almost a decade.[9,10] Recently, a carefully designed and controlled study in patients with myocardial infarction has demonstrated the ability of timolol to reduce sudden cardiac death by approximately 45% over a 2-year period.[11] On the basis of this study, timolol has been approved by the Food and Drug Administration for prophylaxis of cardiac death in patients with recent infarction. Whether this protective effect is specific to certain agents such as timolol or a general effect of the beta-adrenergic blocking agents has not been established. Beneficial effects of other beta-adrenergic agents such as metoprolol and propranolol have been suggested by subsequently reported studies.[12,13]

Despite this clinical evidence for a cardioprotective effect of at least certain beta-adrenergic blocking agents, the mechanism of action remains obscure. An antiischemic effect is well established; however, most episodes of sudden cardiac death are unassociated with excessive cardiac demand, history of anginal acceleration, or myocardial infarction.[1] Even transient decreases

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in coronary flow however, may be associated with decreases in VF threshold in animal models.[1,14] Platelet aggregation and coronary spasm have been proposed as mechanisms causing transient coronary hypoperfusion.[15,16] Propranolol has weak antiplatelet activity,[17] but this has not been shown to be clinically important. Aspirin, an established antiplatelet drug, does not reduce sudden cardiac death in coronary patients.[18] Beta-blocking drugs are ineffective against coronary spasm and may in fact exacerbate vasotonic angina.[19] An antiarrhythmic effect (suppression of ventricular ectopy) also appears unsatisfactory as a single mechanism because beta-blocking drugs show relatively weak antiectopic activity in comparison with class I drugs.[20] However, a beneficial effect of these agents on VF threshold is a potential mechanism of action that has been inadequately explored.[21] Little is known about the experimental antifibrillatory effects of beta-adrenergic blocking drugs, and no information is available on comparative effects among these agents.

This study was designed to assess the importance of antifibrillatory effects of the beta-adrenergic blocking drugs in a previously validated canine model.[22] The study was designed to address several questions: What quantitative effects on VF threshold occur, and what is the nature of the dose-response curve? Are any antifibrillatory effects agent- or class-specific?[23] Are accessory drug characteristics of importance in determining antifibrillatory potential?[24,25] Are effects explained by interruption of cardiac sympathetic stimulation?

Methods

Mongrel dogs of both sexes, weighing 15 to 25 kg, were anesthetized with pentobarbital sodium (30 mg/kg), intubated, and artificially ventilated with room air. Electrocardiographic limb leads were attached and monitored continuously on an oscilloscope. A cutdown was performed on a femoral artery and vein, an arterial pressure line established for blood pressure monitoring, and a venous infusion catheter placed for crystalloid and drug administration. The chest was opened using cautery and shears and the heart isolated and suspended in a pericardial cradle. Bipolar epicardial hook electrodes were placed in the right atrium and right ventricle (outflow tract). The sinus node was crushed and atrioventricular sequential pacing (cycle length 400 ms) initiated. Internal defibrillator leads were inserted into the left ventricular apex and the right atrial appendage and secured with pursestring sutures. Pacing studies were performed with the use of a custom 4-channel programmable stimulator coupled to a multichannel oscilloscope and recorder. The left anterior descending coronary artery was dissected free in its midportion and a lubricated umbilical tape tunneled underneath. The umbilical tape could then be used to temporarily occlude the vessel. A stainless steel, bipolar hook electrode with interelectrode separation of 3 mm was attached epicardially at the right ventricular septum, bordering the potential ischemic zone, and used to deliver the VF pulses. A bipolar plunge electrode was placed through the left ventricular mid-anterior wall 5 cm from this electrode.

Determination of VF threshold: This determination was performed with modification of a previously described method.[14,22,26] Animals were paced from the atrium at a constant cycle length of 400 ms. Four millisecond fibrillation pulses of 60 Hz frequency and 180 ms total duration were synchronized to the atrioventricular pacing stimuli so as to scan the T wave in the vulnerable period of the heart. The same delay after the basic drive stimulus (100 to 150 ms) was used throughout testing in any 1 animal. Current delivered was measured exactly by recording voltage decrease across a precision 1,000 Ω resistor in series with the electrodes. Current intensity was increased in 0.5 mA increments to 5 mA, 1 mA increments to 10 mA, 2 mA increments to 20 mA, 5 mA increments to 50 mA, and 10 mA increments to 100 mA, or until ventricular fibrillation developed. Stimulus trains were delivered after every ninth basic drive cycles, and 3 trains were delivered at each current level. The current intensity inducing sustained VF was defined as the VF threshold. When VF occurred, the heart was immediately defibrillated using a capacitor discharge direct current impulse of 15 J applied through the internal defibrillator leads. The heart was allowed to recover for a minimum of 15 minutes.

The schedule for determination of VF threshold was as follows: Before drug administration, a control determination was made in the absence of ischemia. After a 15-minute rest interval, the mid-anterior descending coronary artery was occluded and threshold determinations during ischemia ("ischemic thresholds") made after 3 minutes. The ligature was released and the heart promptly defibrillated. An initial dose of drug (or saline solution) was administered and VF thresholds repeated without and with ischemia, beginning at 15 minutes. The second and subsequent serial dilutions of drug (or saline solution) were administered and testing repeated in a similar fashion. Normal saline solution was infused at a rate sufficient to maintain blood pressure in the range of pre-drug control readings over the period of study. In several animals, the decay kinetics of elevations in VF threshold were explored by further determinations 1 and 2 hours after the final dose of drug.

Repetitive ventricular response threshold: The currents at which 2 and >2 premature complexes were elicited by the fibrillation pulse were defined as the thresholds for single and multiple repetitive ventricular responses.

Ventricular effective refractory period: The left ventricular effective refractory period was defined as the longest premature interval at which a single premature impulse consistently failed to cause ventricular depolarization. Premature stimuli (S_2) were introduced at twice diastolic threshold after every third paced beat through the plunge bipolar electrode in the left ventricle. Refractory periods were determined to the nearest 1 ms. Evaluations were made just before determinations of VF threshold. Ventricular activation times were measured as the time interval from onset of pacing artifact introduced through the left ventricular plunge electrode to that recorded in the right ventricular electrode 5 cm distant, as measured on a strip chart, paper speed 200 mm/s.

Drug testing: Five beta-adrenergic blocking agents with differing accessory properties (Table I) were selected for study and obtained from commercial sources: timolol (Merck, Sharp and Dohme, West Point, Pennsylvania), pindolol (Sandoz, East Hanover, New Jersey), propranolol (Ayerst, New York, New York), metoprolol (Geigy Pharmaceuticals, Summit, New Jersey), and labetolol (Shering, Bloomfield, New Jersey). Drugs were solubilized and buffered to a physiologic pH when necessary and diluted in normal saline solution to allow convenient administration of doses of 0.003 to 1.0 mg/kg. Doses were calculated on the basis of an average animal weight of 20 kg. Increments of 0.003, 0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg were used. Drugs were typically administered in volumes of 1 to 25 ml. Control animals were given an equivalent volume dose of saline solution at each dosing time.

TABLE I Pharmacologic Properties of Some Beta-Blocking Drugs*

Drug	Membrane Stabilizing	Cardio-selectivity	Partial Agonist	Alpha-Blocking
Propranolol	++	0	0	0
Timolol	0	0	±	0
Metoprolol	±	+	0	0
Pindolol	+	0	+++	0
Labetolol	+	0	0	+

* Modified from Frishman.[24]
0, +, ±, ++, +++ = range of drug effect intensity, where 0 = no effect and +++ = very strong effect.

Stellate ganglionectomy: In selected animals, both right and left stellate ganglia were identified near the apex of each pleural cavity and dissected free. After control VF threshold determinations, all branches of each ganglion were transected and the ganglia removed. Determinations were repeated. Timolol, 0.01 mg/kg, was administered and the VF threshold determined again.

Analysis of data: Electrophysiologic variables were averaged and are presented as mean ± standard deviation for each separate group of animals. Differences in mean responses between 2 groups were analyzed with Student's *t* test. Analysis of variance was used to assess differences among 3 or more data sets. Paired *t* testing was used to compare responses in the same animal under 2 different conditions. Significance was assumed at a probability (p) level of <0.05 for 2-tailed hypotheses. For purposes of analysis, a VF threshold of 110 mA was assigned in cases in which the measurable threshold (100 mA) was exceeded.

Results

Control VF thresholds: Ventricular fibrillation threshold averaged 11.7 ± 7.6 mA in 46 animals during control nonischemic testing. During control ischemic testing, the average fibrillation current was reduced to 7.0 ± 7.4 mA ($p < 0.01$ versus nonischemic).

VF threshold response over time (saline control): Nine animals subsequently given saline solution alone showed a flat VF threshold response with time, during both nonischemic and ischemic conditions (Fig. 1, Table II).

VF threshold response to timolol (Fig. 1, Table II): In contrast, VF thresholds were augmented substantially after as little as 0.003 mg/kg timolol in 10 dogs and increased further after 0.01 mg/kg to 71 ± 33 mA for nonischemic and 38 ± 37 mA for ischemic conditions, representing 3- to 6-fold increases. The large standard deviations point to substantial animal-to-animal variation in response. However, differences after 0.01 mg/kg for nonischemic threshold compared with predrug control values or to the saline response at a similar time point were highly significant ($p < 0.001$). Threshold increases during ischemia were significant in comparison with saline solution and pre-drug control at levels of $p < 0.01$ and $p < 0.05$, respectively.

VF threshold response to pindolol (Fig. 1, Table II): A substantial increase in VF threshold occurred after pindolol in 7 dogs, and these increases were highly significant. A maximal response was achieved at a dose of 0.1 mg/kg; the VF threshold averaged 81 ± 32 mA without and 46 ± 31 mA with ischemia, a 7-fold or greater increase. These peaks differed significantly from concurrent saline solution ($p < 0.001$) and from initial predrug control responses ($p < 0.005$ for nonischemic and $p < 0.02$ for ischemic conditions).

Response of VF threshold to propranolol (Fig. 2, Table II): After propranolol, VF threshold in 7 animals increased more gradually than after timolol or pindolol to plateau after 0.3 mg/kg at 58 ± 27 mA without and 36 ± 11 mA with ischemia, a 5-fold or greater increase. Differences between peak values and initial control measurements ($p < 0.01$, $p < 0.001$) and parallel saline controls ($p < 0.002$, $p < 0.001$) were highly significant under both nonischemic and ischemic conditions, respectively.

Response of VF threshold after metoprolol (Fig. 2, Table II): The response of VF threshold after metoprolol in 7 animals is given in Figure 2. VF threshold continued to increase until after doses of 0.3 to 1.0 mg/kg. After 1 mg/kg, threshold averaged 60 ± 28 mA

TABLE II Optimal Ventricular Fibrillation Responses

Drug	Dose (mg/kg)	VFT (mA) Nonischemic (Mean ± SD)	VFT (mA) Ischemic (Mean ± SD)
Saline (control) (n = 9)	0 (25 ml)	11.8 ± 7.0 11.8 ± 10.6	7.2 ± 4.4 8.9 ± 7.3
Timolol (n = 10)	0 0.01	14.4 ± 10.0 70.6 ± 32.6‡,¶	12.4 ± 13.2 38.3 ± 37.1*,‖
Pindolol (n = 7)	0 0.1	10.9 ± 6.6 80.8 ± 32.2†,¶	5.2 ± 1.4 46.3 ± 30.8*,¶
Propranolol (n = 7)	0 0.3	10.7 ± 8.9 57.9 ± 26.6†,‖	4.1 ± 1.9 35.8 ± 10.7‡,¶
Metoprolol (n = 7)	0 1.0	10.4 ± 7.7 60.0 ± 28.1*,¶	3.1 ± 2.2 40.2 ± 43.4§
Labetolol (n = 6)	0 1.0	10.5 ± 3.6 66.8 ± 35.5*,¶	7.8 ± 5.7 52.4 ± 34.3*,‖
Beta-blocker (n = 37)	0 Optimum	11.6 ± 7.8 66.8 ± 30.4‡,¶	6.9 ± 8.1 42.4 ± 30.9‡,‖

* $p < 0.05$ versus predrug.
† $p < 0.01$ versus predrug.
‡ $p < 0.001$ versus predrug.
§ $p < 0.05$ versus 25 ml saline solution.
‖ $p < 0.01$ versus 25 ml saline solution.
¶ $p < 0.001$ versus 25 ml saline solution.
SD = standard deviation; VFT = ventricular fibrillation threshold.

TABLE III Summary of Optimal Doses of Beta-Blocking Drugs

Drug	VFT (mg/kg)	Beta-Blockade Potency Ratio[24]
Timolol (n = 10)	0.01	6
Pindolol (n = 7)	0.1	6
Propranolol (n = 7)	0.3	1 (0.2 mg/kg)
Metoprolol (n = 7)	1.0	1
Labetolol (n = 6)	1.0	0.3

VFT = ventricular fibrillation threshold.

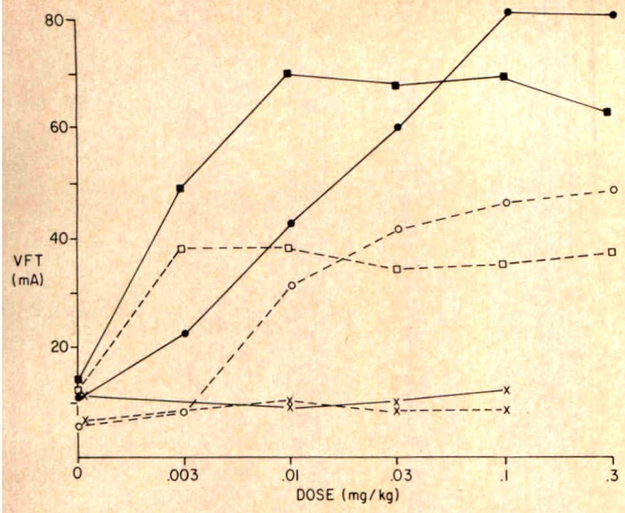

FIGURE 1. Effects on ventricular fibrillation threshold (VFT) of incremental dosing with timolol (**squares**), pindolol (**circles**), or saline solution (**X**). The VF threshold in milliamps is shown on the vertical axis and the drug dose (for timolol, pindolol) on the horizontal axis; the response to drug is compared with time-concurrent saline controls. Measurements during ischemia are represented by **open symbols connected by dashed lines**. Those without ischemia are represented by **solid symbols and lines**. See Table II and text for additional details.

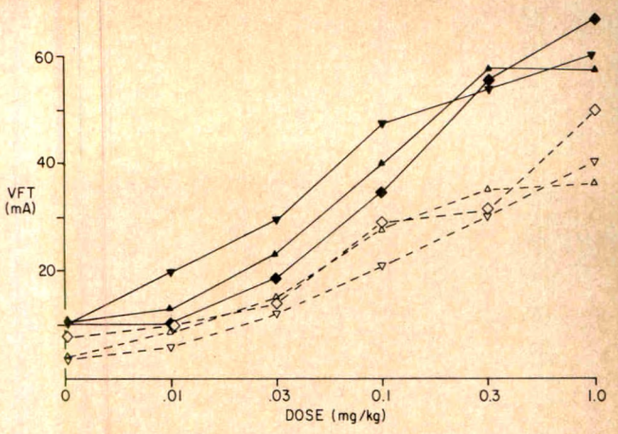

FIGURE 2. Effect on ventricular fibrillation threshold (VFT) of incremental dosing with labetolol (**diamonds**), metoprolol (**wedges**), and propanolol (**triangles**). The format is similar to that in Figure 1, except that saline controls are not redrawn.

without and 40 ± 43 mA with ischemia, a ≥6-fold increase. Again, interanimal variation was great, particularly during ischemia. Differences between drug and saline responses were significant at $p < 0.001$ for nonischemic and $p < 0.02$ for ischemic conditions. The nonischemic value differed from its initial control at a level of $p < 0.02$.

Response of VF threshold to labetolol (Fig. 2, Table II): Labetolol caused increases in VF threshold after approximately 0.1 mg/kg. After 1 mg/kg, VF threshold averaged 67 ± 36 mA without and 52 ± 34 mA with ischemia, a 6-fold increase. The peak effect differed from concurrent saline control at significance levels of $p < 0.001$ and $p < 0.01$ (nonischemic, ischemic conditions) and from initial control values at $p < 0.02$.

Summary of beta-blocker effects on VF threshold (Tables II and III): Each beta-blocking drug augmented VF threshold to similar maximal levels, averaging 67 ± 30 mA without and 42 ± 31 mA with ischemia, a 6-fold increase (Table II). However, the doses at which optimal effects were achieved varied widely. The order of potency generally paralleled that of known beta-blocking potency (Table III). Also, maximal effects were generally achieved at doses known to provide full beta-blockade. However, it can be noted that timolol caused maximal effects at lower apparent relative doses, for example, at one tenth that of pindolol, which is said to have equivalent beta-blocking potency.[24]

Response of VF threshold during stellate ganglionectomy: In 3 animals, bilateral stellate ganglion resection led to variable increases in VF threshold (Fig. 3). Subsequent administration of timolol (0.1 mg/kg) led to further modest to substantial increases in VF threshold, to levels provided by the beta-blocking drug alone (compare with Figure 1).

Repetitive ventricular response thresholds (Table IV): Increases in repetitive responses paralleled those in VF threshold. Thresholds for appearance of multiple nondriven repetitive ventricular responses (m-RVR) increased 6-fold after optimal doses of beta-blocking drugs for both nonischemic and ischemic conditions but did not change after saline solution. Differences in drug versus saline response were significant ($p < 0.001$, $p < 0.05$). Nonischemic m-RVR threshold averaged 8.6 mA before and 53.8 mA after therapy ($p < 0.001$). During ischemia, m-RVR threshold averaged 5.6 mA before and 35.9 mA after therapy ($p < 0.001$). Increases in m-RVR threshold also reached significance during nonischemic and ischemic conditions for each individual drug.

Thresholds for appearance of single nondriven repetitive ventricular response (s-RVR) increased 8- to 10-fold after optimal doses of beta-blocking drugs

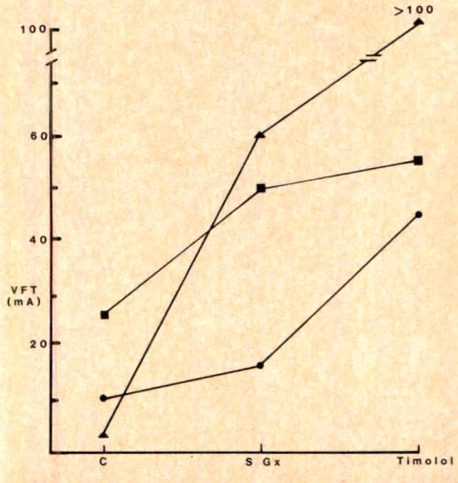

FIGURE 3. Effects of sequential bilateral stellectomy and beta blockade with timolol, 0.1 mg/kg, in 3 dogs. C = control study; SGX = stellate ganglionectomy. VFT = ventricular fibrillation threshold.

TABLE IV Therapeutic Effects on Repetitive Ventricular Response Thresholds

Drug	Dose (mg/kg)	m-RVR Threshold		s-RVR Threshold	
		Nonischemic	Ischemic	Nonischemic	Ischemic
Saline (control)	0	7.7 ± 4.3	6.1 ± 3.5	3.8 ± 4.2	3.8 ± 3.1
	(25 ml)	10.6 ± 9.5	8.7 ± 7.2	7.8 ± 6.6*	6.6 ± 5.6
Timolol	0	12.0 ± 9.7	9.7 ± 12.3	4.7 ± 7.7	5.0 ± 9.0
	0.01	56.1 ± 29.0‡,¶	34.4 ± 32.9*	23.8 ± 20.7†,‖	17.9 ± 16.1*,§
Pindolol	0	7.4 ± 5.7	4.3 ± 3.9	2.0 ± 1.9	3.8 ± 4.2
	0.1	62.5 ± 26.2†,¶	42.3 ± 33.4*,§	27.8 ± 11.4‡,‖	22.7 ± 9.2†,‖
Propranolol	0	8.5 ± 9.9	3.5 ± 1.6	1.6 ± 1.0	2.4 ± 1.3
	0.3	48.1 ± 20.0†,¶	24.9 ± 12.7†,§	27.9 ± 15.6†,‖	20.6 ± 11.7†,§
Metoprolol	0	6.6 ± 6.1	3.1 ± 2.2	1.1 ± 0.6	2.1 ± 1.9
	1.0	53.2 ± 32.4*,‖	44.6 ± 41.7*,§	53.4 ± 37.2*	23.6 ± 18.9*,¶
Labetolol	0	6.8 ± 3.4	6.9 ± 5.5	2.4 ± 2.9	3.7 ± 3.3
	1.0	47.8 ± 37.1*,§	37.4 ± 25.9*,§	33.8 ± 13.3†,‖	29.8 ± 18.5†,‖
Beta-blocking drugs	0	8.6 ± 7.7	5.6 ± 7.3	2.3 ± 4.3	3.7 ± 5.4
	Optimum	53.8 ± 27.3‡,¶	35.9 ± 29.2‡,§	27.4 ± 19.4‡,¶	21.8 ± 15.9‡,¶

* $p < 0.05$ versus predrug.
† $p < 0.01$ versus predrug.
‡ $p < 0.001$ versus predrug.
§ $p < 0.05$ versus 25 ml saline solution.
‖ $p < 0.01$ versus 25 ml saline solution.
¶ $p < 0.001$ versus 25 ml saline solution.
s-RVR = single, multiple repetitive ventricular responses.

(Table IV). Nonischemic single-RVR thresholds averaged 2.3 mA before and 27.4 mA after therapy ($p < 0.001$). Responses during ischemia were similar. Increases in s-RVR threshold were also significant for each individual drug. In the saline control group, small increases with repeated testing were noted, but comparisons of saline versus drug therapy at similar times showed significant differences for both ischemic and nonischemic conditions ($p < 0.02$).

Time-decay in augmentation of VF threshold and m-RVR: One hour after the final beta-blocking drug dose, VF thresholds had declined by 14.0 ± 19.6 mA ($p < 0.005$, n = 23 pair) for nonischemic and by 11.4 ± 21.8 mA ($p < 0.05$, n = 20 pair) for ischemic conditions. After 2 hours, VF threshold had decreased an average of 25.4 ± 22.0 mA ($p < 0.001$, 17 pair) for nonischemic and 18.3 ± 28.0 mA ($p < 0.02$, 16 pair) for ischemic conditions. One hour after the final beta-blocking drug dose, multiple-RVR threshold had declined by 12.3 ± 20.3 mA ($p < 0.02$, n = 20 pair) for nonischemic and 9.6 ± 19.5 mA ($p < 0.05$) for ischemic conditions. After 2 hours, m-RVR threshold had decreased an average of 21.1 ± 25.4 mA ($p < 0.005$, n = 18 pair) for nonischemic and 14.5 ± 27.8 mA ($p < 0.05$) for ischemic conditions.

Ventricular activation times: Activation times, reflecting ventricular conduction between the left ventricular plunge electrode and the right septal electrode, averaged 63.3 ± 11.5 ms in the control study without ischemia and 64.1 ± 12.7 ms with ischemia (n = 38), an insignificant change. During repeated measurements over time in the saline control group, no change occurred. During incremental administration of beta-blocking drugs, a gradual small increase in activation time was observed. Comparing measurements for optimal doses of each drug with control measurements, this increase averaged 6.2 ± 8.9 ms ($p < 0.002$). Significant increases in activation time for individual drugs were also noted for labetolol (nonischemic and ischemic), propranolol (nonischemic), and timolol (ischemic conditions).

Ventricular refractory periods: During the control study, left ventricular effective refractory period averaged 194 ± 19 ms (n = 36) without ischemia and 199 ± 20 ms with ischemia (p = not significant). In the saline control group, small variable changes over time (usually increases) were not significant. During incremental dosing with beta-blocking drugs, gradual increases in refractory periods were noted. After optimal drug dosing, effective refractory period increased by 29 ± 17 ms (n = 27, $p < 0.001$) for nonischemic and by 20 ± 16 ms (n = 26, $p < 0.001$) for ischemic conditions. Significant increases were also noted in refractory periods by paired analysis for each drug. Similar increases in refractory period were induced by stellectomy alone (23 ms, n = 5), and the addition of timolol did not lead to a further change. Refractory period increases thus appear to reflect antisympathetic effects.[27]

Blood pressure responses: Initial mean blood pressures averaged 82 ± 32 mm Hg. With time, blood pressure in the control (saline) and beta-blocking drug treatment groups showed insignificant and similar declines of 3.0 and 3.4 mm Hg at the end of optimal dosing. Adequate hydration and constant rate pacing were thus effective in preventing a relative decrease in blood pressure in the treatment versus control group.

Discussion

Our study documents substantial antifibrillatory effects of intravenously titrated beta-adrenergic blocking agents in an open chest, anesthetized dog model. The 5 agents tested possess a variety of accessory characteristics, but in full beta-blocking doses each was effective in augmenting VF threshold, including thresholds during acute ischemia, an average of 6-fold. Although a precise relationship of VF threshold augmentation and beta-blockade was not determined in this study, a generally parallel order of potencies was shown (Table III). Repetitive ventricular response thresholds, viewed as another index of antifibrillatory

effect,[1,22,28] were augmented in parallel with VF thresholds. Dependence of VF threshold on cardiac sympathetic stimulation was suggested by results of bilateral stellate ganglionectomy. The resulting increase in fibrillation threshold after stellectomy confirms recent experimental observations of Schwartz and Stone[29] and earlier observations by Kliks et al.[14] That further augmentation in threshold followed timolol suggests additional effects which may include blockade of circulating cathecholamines and blockade of residual cardiac sympathetic innervention; nonbeta-blocking pharmacologic actions appear to be a less likely explanation.[25]

A consensus has not yet been reached as to whether the preventive action of certain beta-blocking drugs on clinical sudden death represents a class or individual drug effect. Currently, the Food and Drug Administration requires each beta-blocking drug to submit to individual testing before approval is considered for the indication of prophylaxis of cardiac death. Our observations provide insight about the effect of accessory properties on experimental VF threshold augmentation. If membrane stabilizing (class I antiarrhythmic) properties were important, propranolol should show a relative advantage in dose or maximal effect over timolol. This was not noted, and a relative dose advantage of timolol could in fact be argued. Higher dose propranolol ($\geq$1 mg/kg) did not increase VF threshold further. The cardioselectivity of metoprolol did not appear to afford an advantage (or significant disadvantage). Alpha-blockade may have certain antiarrhythmic potential based on some arrhythmia models. However, labetolol was the least active on a milligram per kilogram basis of the drugs tested. This could be predicted from its relatively weak beta-blocking potency.[30] Pindolol in lowest doses showed less activity than timolol, although both are rated as equivalent in beta-blocking potency.[24] In this regard, recent preliminary observations of others suggest an adverse effect of intrinsic sympathomimetic activity on VF.[31] If the apparent disadvantage we noted for pindolol versus timolol is real, then pindolol's partial agonist activity may provide a plausible explanation. However, in larger doses, excellent antifibrillatory effects of pindolol were noted in our study. Our data are thus consistent with a general "class" effect of the beta-adrenoceptor blocking drugs on VF threshold. This effect presumably relates primarily to blocking effects on the cardiac beta-1 adrenergic receptors, an action that each of these drugs holds in common.

Beta-blocking drug administration also caused small increases in ventricular activation times and effective refractory periods in our model. Refractory period increases were also produced by stellectomy, suggesting antisympathetic effects to be the cause.[27] Ventricular impulse conduction velocity has recently been shown to have complex determinants, depending on depth (epicardial versus endocardial), direction (apical versus basal), and perfusion (ischemia) characteristics.[32] Regional discrepancies in conduction velocities may be more important than absolute velocities in determining propensity for experimental VF. Similarly, heterogeneity of ventricular refractoriness may be more important than average refractory period durations.[33] Beta-blocking drugs may act to "homogenize" heterogeneous sympathetic stimulation to the heart as occurs during ischemia and neurogenic stress.[34,35]

We determined control VF threshold measurements similar to those of other studies which have used the stimulus-train technique; average VF thresholds by this technique have ranged from 5 to 15 mA without ischemia and about 40% less (2 to 10 mA) during ischemia.[14,22,26,36,37] In contrast, methods using single or multiple extrastimuli to induce VF require similar currents during ischemia but higher currents in the absence of ischemia.[1,21,38] In our model, drug augmentation in VF threshold was a consistent and reproducible finding under both conditions.

Application of our experimental findings to the clinical setting must be made with caution. Experimental VF threshold is only 1 of many variables used to define an antiarrhythmic drug's potential for activity on the complex determinants of clinical VF.[39] Open-chest, anesthetized dogs represent a model with high sympathetic stimulation in which beta-blocking drugs may be particularly effective. Effects of various beta-blocking drugs in other models relevant to sudden cardiac death will thus be of interest.[39] However, other drugs that possess clinical antifibrillatory activity (lidocaine, bretylium) also elevate experimental VF threshold.[22,36,40] Elevation in VF threshold should thus be considered a potentially important protective mechanism by which beta-blocking drugs may reduce sudden cardiac death, particularly in the setting of ischemic heart disease. During performance of these studies, protective effects against sudden cardiac death of 3 of the agents tested—timolol, metoprolol, and propranolol—were reported in large scale, carefully designed studies.[11–13]

Recent observations with several antiarrhythmic agents suggest a lack of close correlation between antiectopic and antifibrillatory effects.[41–45] Bretylium, for example, is an excellent antifibrillatory drug but a poor antiectopic agent.[40,42,43] Similarly, lidocaine may exert antifibrillatory effects in instances in which antiectopic and antitachycardic actions are ineffective.[44,45] A model suggesting an explanation for lidocaine's action in this instance was recently presented[45]; microreentrant conditions necessary for VF may be prevented in situations in which macroreentry (ventricular tachycardia) or automatic or nonsustained reentrant ectopy is not.

Primary antifibrillatory action has been associated most strongly with a separate class (class III) of antiarrhythmic agents.[46,47] A member of this class, amiodarone, has also recently been postulated to be of positive benefit in preventing recurrent VF.[48] Induction of ventricular tachycardia by programmed ventricular stimulation can occur with either amiodarone or bretylium at a time when clinical control of recurring episodes of VF is manifest,[49,50] again drawing a distinction between effects on microreentrant VF and macroreentrant ventricular tachycardia or ectopic mechanisms.

In the past, inadequate studies have been performed to assess the antifibrillatory role of beta-blocking drugs, although individual studies have suggested experi-

mental antifibrillatory benefit for certain beta-blocking drugs.[21,23] However, the results of our study suggest that beta-blocking drugs as a group may possess antifibrillatory action which is of similar magnitude for optimal doses of each agent. The major effect of beta-adrenergic blocking drugs in increasing VF threshold in our experimental model appears to be best explained by blockade of cardiac beta-adrenergic impulses.

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Effects of Exercise and Isoproterenol During Atrial Fibrillation In Patients With Wolff-Parkinson-White Syndrome

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The effects of exercise and isoproterenol on atrial fibrillation (AF) were studied in 17 patients with Wolff-Parkinson-White syndrome (WPW) to assess the risk of developing a rapid ventricular response. Mean cycle length (R-R interval) and shortest R-R interval between both preexcited and nonpreexcited QRS complexes were recorded, as well as the percentage of preexcited complexes during control periods, during bicycle exercise, and during isoproterenol infusion. Exercise resulted in significantly shorter mean cycle length and the shortest R-R interval between nonpreexcited complexes. Exercise also resulted in a significantly lower percentage of preexcited complexes during AF, but had no effect on the R-R intervals between preexcited complexes. Isoproterenol had a variable effect on the percentage of preexcited QRS complexes, but resulted in significant shortening of mean cycle length and the shortest R-R interval between both normal and preexcited complexes. With isoproterenol, 12 of 17 patients had shortest preexcited R-R intervals $\leq$215 ms, compared with 6 of 17 in the control state. Isoproterenol infusion increased the rate of conduction over the accessory pathway during AF and allowed better assessment of the risk of excessively rapid rates occurring during AF. Exercise is not an adequate test for this purpose.

The ventricular response to atrial fibrillation (AF) is of major importance in planning the treatment of patients with Wolff-Parkinson-White syndrome (WPW). In these patients, the functional properties of the accessory pathway determine whether or not excessively rapid ventricular rates are achieved during AF. It has been shown that patients with R-R intervals approaching 200 ms during AF are at risk for the development of ventricular fibrillation.[1,2] A single observation of the ventricular response during AF at rest may be insufficient to fully evaluate the risk faced by a patient with WPW. Changes in autonomic tone occurring during exercise or associated with anxiety or hypotension at the onset of the arrhythmia may influence the functional properties of accessory pathways and significantly affect the ventricular response during AF. To fully assess the potential for the development of life-threatening arrhythmias in patients with WPW, we studied the effects of an isoproterenol infusion and of bicycle exercise during AF. The results of these investigations in 17 patients with WPW are the subject of this report.

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Methods

Patient population: These investigations were carried out as part of the routine electrophysiologic evaluation of patients referred to Duke University Medical Center with symptomatic arrhythmias due to the presence of accessory atrioventricular pathways. All patients were studied in the postabsorptive state after giving informed consent. Small doses of diazepam were occasionally given for sedation.

Seventeen patients are included in this group. All patients had anterogradely functioning accessory pathways located in the left free wall (8 patients), posteroseptal (6 patients), right free wall (2 patients), and antero-septal (1 patient) positions. Only 1 patient failed to demonstrate retrograde function of the accessory pathway.

Bicycle exercise was not performed in 3 patients. Patients were excluded from the study if AF in the control state was associated with an extremely rapid ventricular response causing hemodynamic compromise and requiring cardioversion to terminate the arrhythmia.

Isoproterenol infusion: Atrial fibrillation was induced by rapid atrial pacing through a coronary sinus catheter introduced from the left subclavian vein. All patients were studied without receiving cardiac arrhythmic drugs. A control period of AF was followed by continuous infusion of isoproterenol beginning at an infusion rate of 0.5 μg/min and increasing to 1, 2, 3, and 4 μg/min. The infusion rate was increased every 5 minutes until a rate of 4 μg/min was reached, or until symptoms associated with isoproterenol infusion became intolerable. Blood pressure was monitored frequently. No patient required discontinuation of isoproterenol infusion because of a change in blood pressure or the occurrence of chest pain. At peak isoproterenol infusion, AF was reinduced if sinus rhythm had supervened after the control period.

TABLE I Preexcited QRS Response to Isoproterenol (Shortest R-R Interval)

	Control		Isoproterenol	
Patient	ms	% Preexcited	ms*	% Preexcited†
1	227	38	200	100
2	215	39	165	30
3	210	95	185	50
4	200	100	205	98
5	200	90	170	80
6	270	44	180	91
7	182	72	160	13
8	215	100	150	100
9	220	50	257	44
10	282	17	257	3
11	260	92	178	92
12	290	35	‡	3
13	‡	9	172	45
14	280	75	200	40
15	240	100	252	69
16	278	100	235	57
17	227	90	163	95

* $p < 0.008$.
† $p > 0.1$.
‡ Two consecutive preexcited complexes not seen.

TABLE II Preexcited QRS Response to Exercise (Shortest R-R Interval)

	Control		Exercise	
Patient	ms	% Preexcited	ms*	% Preexcited†
3	210	95	245	42
4	190	100	190	97
5	200	90	180	59
6	270	65	‡	0
7	192	78	330	3
8	215	100	195	100
10	282	48	290	50
11	255	100	220	99
12	390	4	355	12
13	‡	1	‡	4
14	280	11	‡	0
15	240	100	‡	10
16	278	100	267	18
17	227	90	205	75

Exercise was not performed in 3 patients.
* $p > 0.1$.
† $p = 0.008$.
‡ Two consecutive preexcited complexes not seen.

Exercise: After discontinuance of the isoproterenol infusion, no further recordings were made for at least 20 minutes or until baseline sinus cycle length had returned if sinus rhythm supervened. Atrial fibrillation was reinduced for a preexercise control observation and exercise was then begun with the patient in the supine position with a bicycle ergometer at a load of 25 to 50 W and gradually increased to a maximum of 100 W as determined by the patient's physical condition. Exercise was performed to a minimum of 500 W-min and continued until terminated by patient fatigue. Atrial fibrillation was reinduced at peak exercise if sinus rhythm had supervened.

Surface leads I, II, III, V_1, and V_6 were recorded along with the intracavitary atrial electrograms on a Siemans-Elema Mingograf recorder at paper speed of 200 mm/s.

Atrial fibrillation was defined as rapid, disorganized atrial activity with multimorphic atrial electrograms recorded from the right atrium, the coronary sinus, or both, and an irregular ventricular response. The QRS complexes were classified as preexcited only if maximally anomalous QRS morphology was present. The mean R-R interval, shortest R-R interval between preexcited complexes, shortest R-R interval between nonpreexcited complexes, and the percentage of preexcited complexes during a minimum of 1 minute of AF were recorded for each intervention and compared with values obtained for the control period in each patient. The statistical analysis of these paired observations using each patient as his or her own control was performed using the Wilcoxon ranked sum test.

Results

Paired observations of mean R-R interval, shortest R-R interval between preexcited and also between non-preexcited complexes, and the percentage of preexcited complexes were made for each patient before and during isoproterenol infusion and exercise. The shortest R-R intervals between preexcited complexes in the control state and with isoproterenol and exercise are listed in Tables I and II, along with the percentage of preexcited QRS complexes for each intervention.

Effects of isoproterenol: Isoproterenol resulted in a significant shortening of the mean cycle length during AF ($p < 0.01$) (Fig. 1). During the control period, no patient had a mean R-R interval approaching 200 ms. With isoproterenol, 1 patient achieved a mean R-R interval of 195 ms. This patient (Patient 8) was 1 of the 2 patients who had had spontaneous ventricular fibrillation during AF. The other patient (Patient 4) with a history of ventricular fibrillation had a decrease in mean R-R interval from 327 to 248 ms.

Six patients had shortest preexcited R-R intervals of ≤215 msec in the control state, as opposed to 12 patients with isoproterenol, including both patients with histories of spontaneous ventricular fibrillation and 2 others with documented rates >300 beats/min during spontaneous AF before referral (Patients 5 and 7).

One patient (Patient 13) had only 9% preexcited complexes in the control state without any evidence of rapid conduction over the accessory pathway, and yet with isoproterenol preexcited 45% of complexes achieving a shortest R-R interval of 172 ms.

Isoproterenol resulted in a significant shortening of the shortest R-R interval between nonpreexcited complexes ($p < 0.01$). Two patients had R-R intervals of ≤205 ms between nonpreexcited complexes during isoproterenol. Neither patient had a history of ventricular fibrillation. There was no consistent effect of isoproterenol on the percentage of QRS complexes during AF that were preexcited.

Atrial fibrillation terminated spontaneously during isoproterenol infusion in 11 patients and shortly after termination of the infusion in 3. Atrial fibrillation reverted spontaneously to atrial flutter in 1 patient and reciprocating tachycardia in another. In 1 patient, AF persisted beyond the infusion and recovery period.

Effects of exercise: As with isoproterenol, exercise resulted in a significant shortening of the mean R-R interval during AF ($p < 0.01$). The shortening of mean R-R interval seen for the entire group was similar with exercise and isoproterenol (72 and 72 ms, respectively). Patient 8, who had had spontaneous ventricular fibrillation during an episode of AF, achieved a mean R-R

interval of 196 ms during exercise (234 ms during control). This patient had also demonstrated similar shortening of mean R-R interval with isoproterenol (195 ms). This patient's QRS complexes were all maximally preexcited during AF in the control, exercise, and isoproterenol periods.

There was no significant change in the shortest R-R interval between preexcited QRS complexes with exercise. Four patients had shortest preexcited R-R intervals of ≤205 ms with exercise, including both patients with histories of spontaneous ventricular fibrillation; however, all 4 patients had shortest preexcited R-R intervals of ≤227 ms (3 under 200 ms) in the control period.

Exercise caused a significant shortening of R-R intervals between non-preexcited complexes ($p < 0.01$). The shortest nonpreexcited R-R interval seen was 215 ms, occurring in a patient with no history of rapid ventricular response to AF.

In contrast to isoproterenol, exercise caused a significant decrease in the percentage of preexcited QRS complexes ($p < 0.01$), with a change in the group means from 70% preexcited complexes in the control state to 41% with exercise. The change in percentage of preexcited complexes was variable among patients, however, with 3 patients increasing the percentage of preexcited QRS complexes by only 3, 8, and 2%, respectively. Atrial fibrillation reverted spontaneously during exercise in 11 patients and shortly after exercise termination in 3 patients.

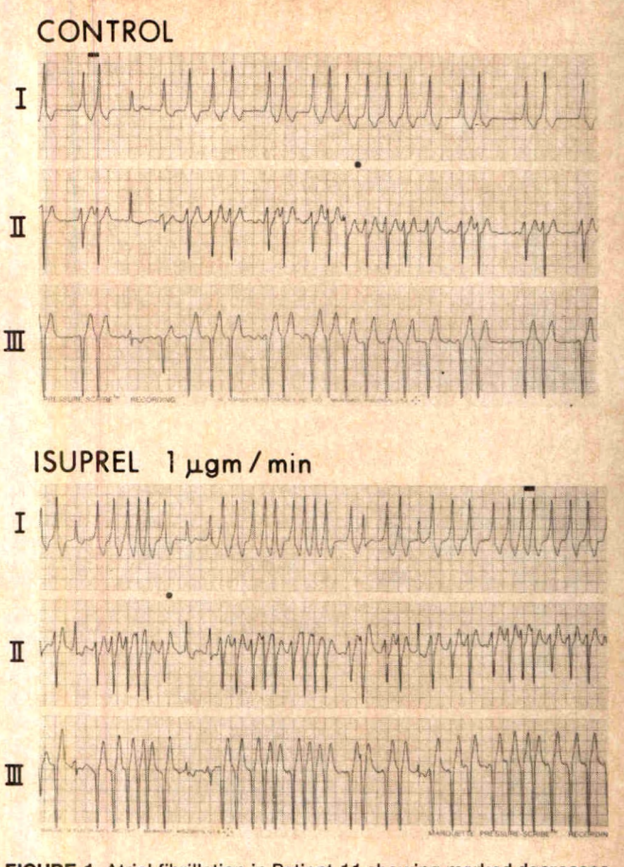

FIGURE 1. Atrial fibrillation in Patient 11 showing marked decreases in mean cycle length (R-R interval) and shortest interval between preexcited complexes during isoproterenol infusion. Nonpreexcited complexes are present before and during isoproterenol.

Discussion

The possibility of the development of a rapid ventricular response to spontaneous AF is of major concern in advising patients with WPW. The natural history of arrhythmias in these patients is sufficiently variable to preclude a confident assessment of this risk even in patients who have not previously demonstrated spontaneous AF. A previous study[3] demonstrated the ineffectiveness of exercise testing in inducing spontaneous arrhythmias in these patients, and the normalization of the preexcited QRS complex with exercise is also well known. This finding may represent rate-related block in the accessory pathway in some patients but more commonly is due to the vagolytic effect of exercise in enhancing atrioventricular nodal conduction. For this reason, exercise would not be expected to provide a reliable test of the risk an individual with WPW faces for rapid ventricular rates during AF. A large reduction in preexcited QRS complexes with exercise does not exclude a rapid ventricular response with isoproterenol. In our study, 10 patients had a reduction with exercise in the percentage of preexcited QRS complexes during AF. Of these 10, five reduced the percentage of preexcited complexes dramatically, with 2 becoming totally nonpreexcited, 2 going from 100% preexcited to 10% and 18%, and 1 going from 78 to 3%. With isoproterenol, however, these patients had preexcited QRS complexes showing shortest R-R intervals of 180, 160, 200, 252, and 235 ms.

The variability of changes in preexcitation in response to exercise may reflect a variety of factors, including the baseline state of autonomic tone, the relation between the refractory periods of the accessory pathway and the atrioventricular node, and the location of the pathway. The balance between vagolytic and sympathetic effects during exercise and the degree of physical training of the individual may also play a role.

Enhanced atrioventricular nodal conduction during exercise may permit retrograde concealed conduction into the accessory pathway. This would result in the failure of anterograde conduction down the accessory pathway, and thereby produce normalization of the QRS complex without any direct effect on accessory pathway refractoriness.

Because of the small number of right-sided and anteroseptal pathways in this group, we cannot make any conclusions regarding the effect of pathway location on R-R intervals during AF.

Isoproterenol produces a shortening of atrioventricular nodal refractoriness and enhances atrioventricular nodal conduction.[4] Wellens et al[5] reported a correlation between accessory pathway refractoriness and ventricular rate during AF, and recently reported shortening of the anterograde refractory period of accessory pathways with isoproterenol.[6] We observed both a shorter mean cycle length and shorter R-R intervals

between preexcited complexes with isoproterenol. Although there was no consistent effect on the percentage of preexcited complexes during AF, 1 patient dramatically increased the percentage of preexcited complexes with isoproterenol. The shortest R-R interval between non-preexcited complexes was also significantly shortened suggesting a uniform effect of isoproterenol on enhancing conduction down both the atrioventricular node and accessory pathway.

Our study confirms previous observations[3] that exercise frequently results in a less preexcited QRS in patients with WPW and demonstrates that this holds true during AF as well. This limits the usefulness of exercise as a means of assessing the risk of a rapid ventricular response in patients with WPW. Although many patients who display very short (≤200 ms) R-R intervals between preexcited complexes during AF with isoproterenol also have relatively short R-R intervals in the control period (≤230 ms), some patients may have few or no preexcited complexes during AF and yet with isoproterenol may preexcite a significant number of complexes and achieve very short R-R intervals. The absence of rapid preexcited ventricular rates during AF in the presence of isoproterenol probably implies a low risk for the spontaneous occurrence of ventricular fibrillation. The usefulness of esophageal pacing as a noninvasive means of inducing AF in the evaluation of these patients has recently been reported.[7]

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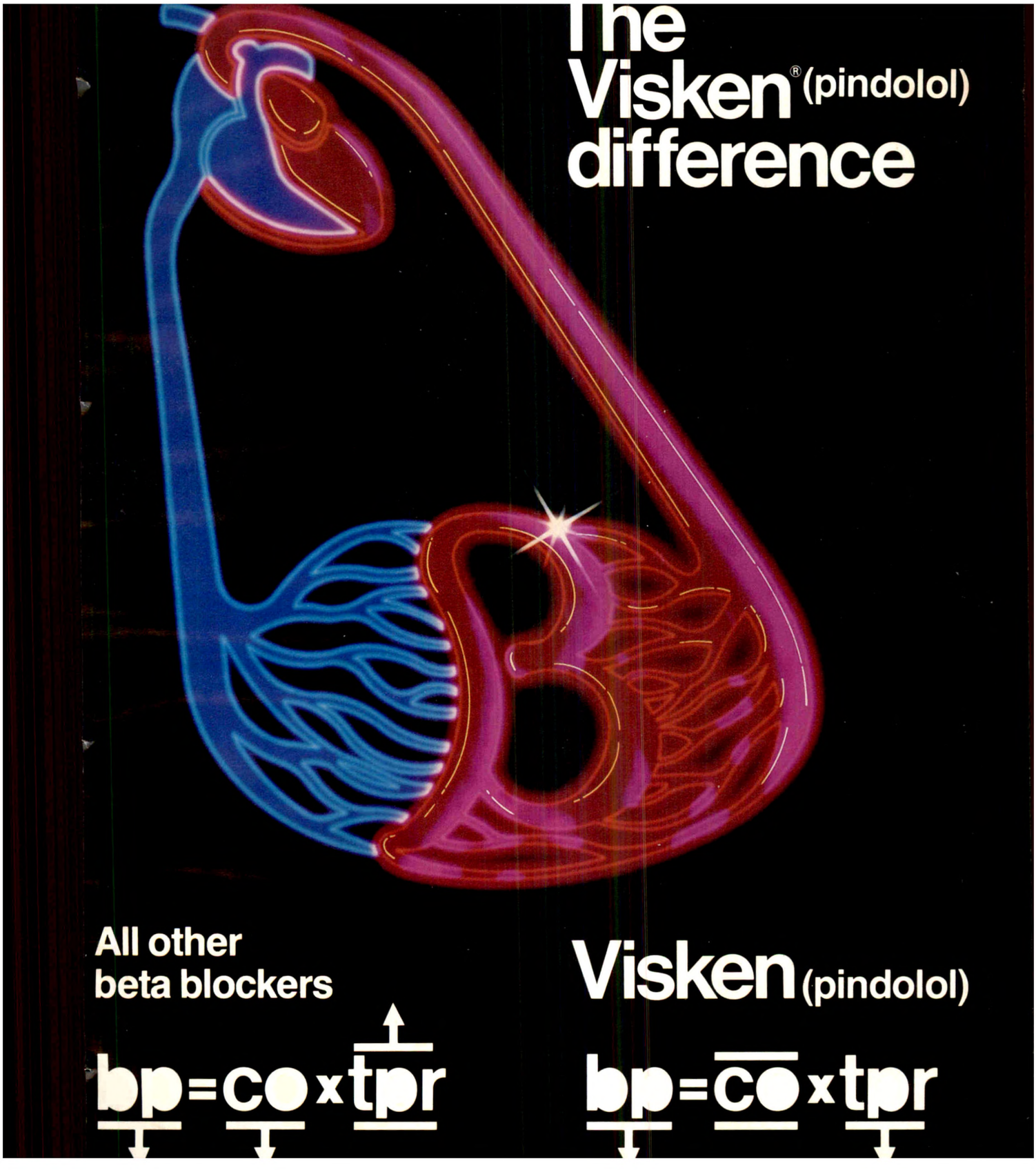
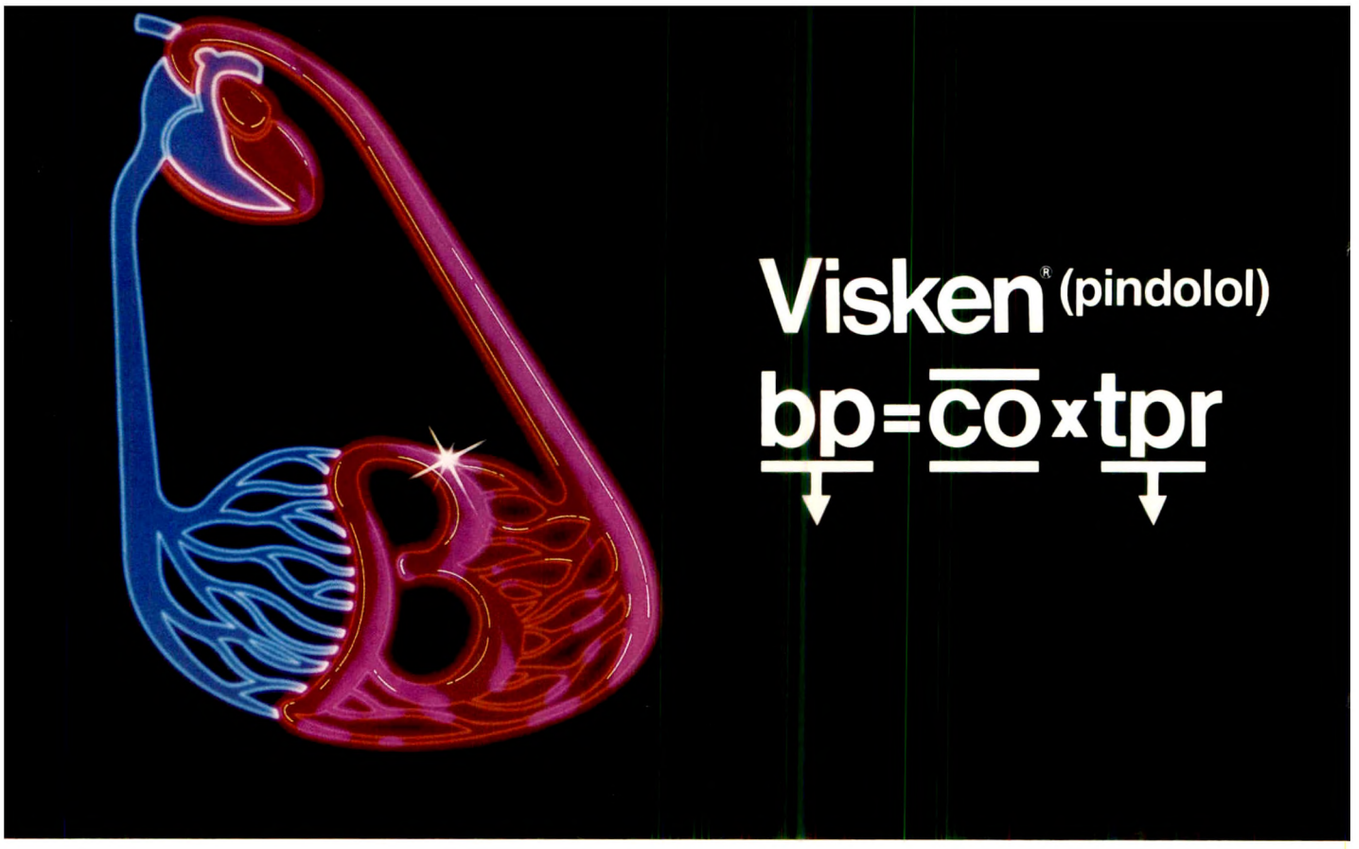

The Visken® (pindolol) difference
All other beta blockers
bp = co x tpr
Visken (pindolol)
bp = co x tpr



Makes hemodynamic sense in the treatment of hypertension

Reduces blood pressure

It's as effective as propranolol in normalizing blood pressure (dbp ≤ 90 mmHg) when used alone. It's also effective when used in combination with a diuretic.[1]

Has little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) maintains resting cardiac output during long-term therapy. The clinical significance of this has not been evaluated.

Reduces total peripheral resistance*

Visken (pindolol) reduces one of the recognized components of hypertension: increased peripheral resistance.* Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

Reduces exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

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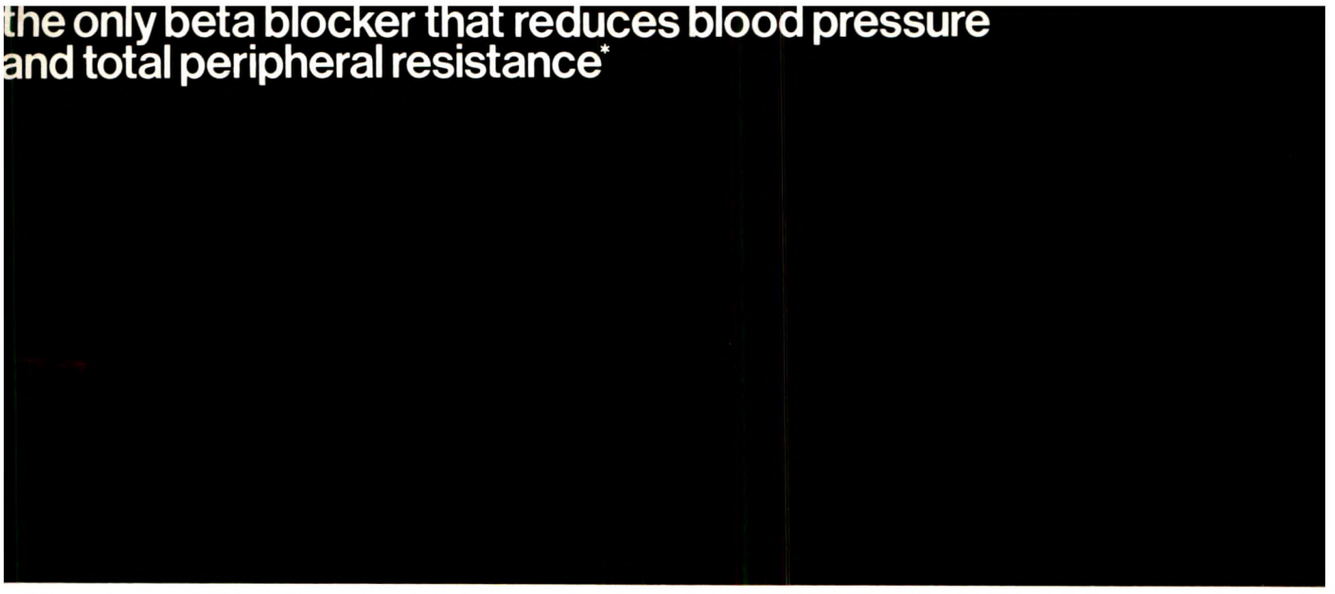
*The clinical significance has not been evaluated. See clinical significance statement on facing page of this advertisement.



Has little effect on resting heart rate

Visken® (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute.

The clinical significance has not been evaluated

The clinical significance of maintaining resting cardiac output, resting heart rate and reduced total peripheral resistance has not been evaluated and there is no evidence or reason to believe that exercise cardiac output is less affected by Visken (pindolol) than other beta blockers.

Maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

Favorable side effect profile

Low incidence of bradycardia

Low incidence of cold extremities

Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

*See clinical significance statement.

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1. Data on file, Sandoz Pharmaceuticals.
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Please see next page of this advertisement for brief summary of prescribing information.

Visken® (pindolol)

Available in 5 mg and 10 mg tablets

Convenient bid dosage

Dosage should be titrated on an individual basis.
Many patients respond to 10-30 mg a day in divided doses.

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elici Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %
Central Nervous System		
Anxiety	4	<1
Bizarre or Many Dreams	8	3
Dizziness	17	23
Fatigue	15	19
Hallucinations	1	0
Insomnia	19	8
Lethargy	3	6
Nervousness	11	5
Weakness	7	5
Autonomic Nervous System		
Paresthesia	5	2
Visual Disturbances	4	3
Cardiovascular		
Dyspnea	9	8
Edema	11	9
Heart Failure	2	<1
Palpitations	2	2
Weight Gain	3	5
Musculo-Skeletal		
Chest Pain	5	3
Joint Pain	11	6
Muscle Cramps	8	2
Muscle Pain	12	12
Gastrointestinal		
Abdominal Discomfort	7	7
Nausea	7	4
Skin		
Pruritus	2	<1
Rash	2	3

*Active Controls: Patients received either propranolol, ∝-methyldopa diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse re were seen in 2% or fewer patients and their relationship Visken (pindolol) is uncertain. AUTONOMIC NERVOUS TEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, cation, cold extremities, heart block, hypotension, sync tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RATORY: wheezing; UROGENITAL: impotence, pollakiu MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have b ported with other beta-adrenergic blocking agents and s be considered potential adverse effects of Visken (pindol

Central Nervous System: Reversible mental depression gressing to catatonia; an acute reversible syndrome cha ized by disorientation for time and place, short-term me loss, emotional lability, slightly clouded sensorium, and creased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with achin sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and n thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischem colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the blocker practolol has not been reported with Visken (pin during investigational use and extensive foreign experien amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overd is available. Therefore, on the basis of the pharmacologi tions of Visken (pindolol), the following general measure should be employed as appropriate in addition to gastric

Excessive Bradycardia: administer atropine; if there is n sponse to vagal blockade, administer isoproterenol cauti

Cardiac Failure: digitalize the patient and/or administer uretic. It has been reported that glucagon may be useful situation.

Hypotension: administer vasopressors, e.g., epinephrin levarterenol, with serial monitoring of blood pressure. (T evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent suc isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an of 500 mg of Visken (pindolol) by a hypertensive patient. pressure increased and heart rate was ⩾80 beat/min. Re was uneventful. In another case 250 mg of Visken (pindo was taken with 150 mg diazepam and 50 mg nitrazepam, ducing coma and hypotension. The patient recovered in 2 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. recommended initial dose of Visken (pindolol) is 10 mg b. alone or in combination with other antihypertensive agent Many patients will respond to 15 mg per day (5 mg t.i.d.) antihypertensive response usually occurs within the first of treatment. If a satisfactory reduction in blood pressure not occur within 2-3 weeks, the dose may be adjusted in ments of 10 mg per day at 2-3 week intervals up to a ma of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages 100. 5 mg tablets embossed "VISKEN 5" on one side, an "78-111" and scored on other side (NDC 0078-0111-05). tablets embossed "VISKEN 10" on one side, and "78-73" scored on other side (NDC 0078-0073-05). [VIS-Z2 9

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East Hanover, NJ 07936

VIS-3

Prevalence and Correlates of Posterior Extra Echocardiographic Spaces in a Free-Living Population Based Sample (The Framingham Study)

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To obtain epidemiologic information on extra echocardiographic spaces immediately posterior to the left ventricular free wall, 2,028 subjects in the original Framingham cohort study (mean age 70 ± 7 years) and 3,624 of the offspring of the cohort (and their spouses) (mean age 44 ± 10 years) with adequate echocardiograms were evaluated. Extra echocardiographic spaces were detected in 370 (6.5%) of the 5,652 subjects. The prevalence ranged from <1% in subjects in the 20- to 30-year age decade to >15% for those in their 80s. Extra echocardiographic spaces tended to be more common in subjects who were older, female, obese, more hypertensive, and who had higher blood sugar levels and higher low density lipoprotein cholesterol levels (measured 8 years earlier). The high prevalence of extra echocardiographic spaces and the independent association with age (cohort and offspring), obesity (cohort and male offspring), and ventricular septal hypertrophy (cohort and male offspring) is compatible with at least 2 hypotheses among others that should be tested: (1) Subepicardial fat may often masquerade as pericardial fluid producing a posterior extra echocardiographic space, especially in obese elderly subjects. (2) Small posterior extra echocardiographic spaces may often be early markers of subclinical hypertensive heart disease.

One of the earliest clinical uses of echocardiography was the diagnosis of pericardial effusion. Echocardiography is now considered the safest, most expedient, and most reliable method for making this diagnosis.[1,2] In the past, extra echocardiographic spaces found anterior to the right ventricular free wall in the absence of such spaces posteriorly were thought to represent fat, whereas posterior extra echocardiographic spaces were usually thought to be pericardial fluid.[2,3] Such effusions could be physiologic (in small amounts) or pathologic.[4] Clinical reports differ regarding the significance of these effusions and their prevalence. Prevalence estimates from these reports range from 5 to 49%.[5–18] Clinical studies have indicated that these echo-poor spaces are frequently associated with various cardiac disorders, including congestive heart failure, pericarditis, myocardial infarction, and hypertensive heart disease among others.[4,19,20] Such echo-poor spaces are also frequently found unexpectedly in patients without overt cardiac disease.[4,19]

Population-based data are lacking regarding these echo-poor spaces. Such data can give prevalence estimates that are less affected by selective bias and might yield clues regarding the pathogenesis of such echo-poor spaces. To this end, echocardiographic studies being conducted in the ongoing prospective population-based Framingham Study were used to assess the prevalence and correlates of extra echocardiographic spaces.

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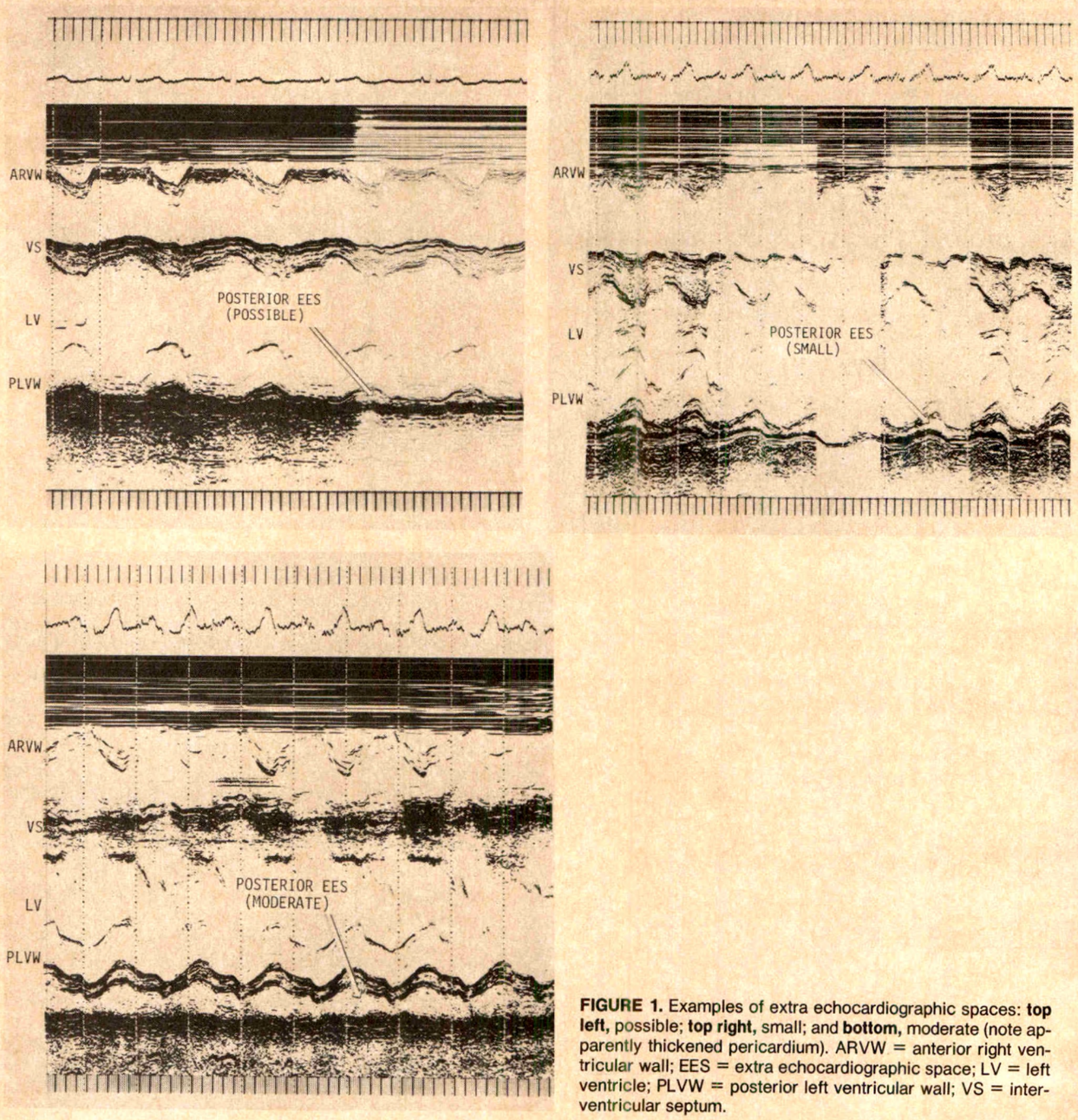

FIGURE 1. Examples of extra echocardiographic spaces: **top left,** possible; **top right,** small; and **bottom,** moderate (note apparently thickened pericardium). ARVW = anterior right ventricular wall; EES = extra echocardiographic space; LV = left ventricle; PLVW = posterior left ventricular wall; VS = interventricular septum.

Methods

Subjects: At the time of this report, 2,287 of the original Framingham cohort (biennial examination 16) and 3,664 offspring (examination 2) of the original cohort (and their spouses) had been studied by M-mode echocardiography. All subjects gave informed consent before the study. Detailed accounts of the sampling procedure for these populations and the clinical methods employed have been reported elsewhere.[21,22] Echocardiograms of adequate quality to assess the area immediately posterior to the left ventricular free wall were obtained in 1,230 female and 798 male subjects in the cohort group (mean age 70 ± 7 years [standard deviation], range 59 to 90). Interpretable echocardiograms were found in 1,871 female and 1,753 male patients in the offspring study group (mean age 44 ± 10 years, range 17 to 77). Quetelet's index (weight in kilograms divided by height in meters raised to the second power) was used as a measure of obesity. Evidence of overt cardiac disease was considered present if there were Framingham criteria for coronary disease, congestive heart failure, hypertensive heart disease, valvular heart disease (such as rheumatic heart disease), or miscellaneous "other" heart diseases (such as cardiomyopathy).[23] Clinical information obtained at the time of echocardiography was used for these diagnoses.

Echocardiographic methods: M-mode echocardiography was performed in the partial left lateral decubitus position with the head of the bed elevated 30°. Standard techniques were employed with the transducer preferentially in the fourth intercostal space parasternally.[24] Care was taken to avoid false-positive recordings secondary to aiming the transducer too medially.[5] Automatic gain control and variable damping

were used to aid in identification of echo-poor spaces posterior to the left ventricular free wall. Spatial orientation was aided by the use of 2-dimensional echocardiography in more than 90% of studies which helped to distinguish the descending aorta from other causes of posterior extra echocardiographic spaces. Two-dimensional echocardiography also aided in placing the cursor for the M-mode echocardiogram to assess the maximal extent of the extra echocardiographic space for semiquantitative classification (see later).

Recordings were made using an Aerotech 2.25 MHz focused transducer, a Hoffrel 201 echocardiograph interfaced with a Honeywell 1856 line scan recorder, and a Jason thermographic printer. A Hoffrel mechanical sector scanner was used for 2-dimensional echocardiograms. Only posterior extra echocardiographic spaces were considered in the present report, because of the poorer resolution of anterior versus posterior structures with the equipment used. The criterion used for a posterior extra echocardiographic space was an echo-poor space immediately behind the posterior left ventricular wall which persisted throughout the cardiac cycle. When such spaces were present throughout only some of the cardiac cycles (and only during systole in other cardiac cycles), the spaces were considered "possible." If a posterior extra echocardiographic space measured ≥10 mm in depth, it was considered moderate in size. Between these extremes, the spaces were defined as small (Fig. 1). Left ventricular wall thickness, left ventricular internal dimensions, and left atrial dimension were measured using previously described echocardiographic methods.[25] Such measures were considered abnormal if they were greater than published 95% confidence limits adjusted for age and body size.[25]

Statistical analyses: Where appropriate, Student's *t* test, the chi-square test, or Fisher's exact test was used to assess statistical significance. To assess the relation of the echo-poor spaces to known risk factors for cardiac disease, univariate and multivariate logistic regression analyses were used. Regression analyses were performed using the maximal likelihood estimation and testing procedure described by Walker and Duncan.[26] Each estimated regression coefficient was tested against the alternate hypothesis that a particular partial coefficient was zero. A test outcome indicates whether the independent variable in question makes a statistically significant contribution to the prediction of an extra echocardiographic space.

The dependent variable used in multivariate analyses was the presence of a posterior extra echocardiographic space, whereas the independent variables were age, sex, Quetelet's index, systolic blood pressure, blood sugar, cigarette use, and serum high and low density lipoprotein cholesterol. In contrast to the current examination data used to assess clinical diagnoses (see earlier), the cardiovascular risk factors used as independent variables (except current age) were measured 8 years before echocardiography was performed.

Results

Posterior extra echocardiographic spaces were found in 370 (6.5%) of the 5,652 subjects. The prevalence

TABLE I Cardiovascular Risk Factors in Framingham Cohort Study Subjects With and Without Extra Echocardiographic Spaces

	Male Subjects				Female Subjects			
Variable	Average Cases (n = 61)	SD	Average Noncases (n = 558)	SD	Average Cases (n = 133)	SD	Average Noncases (n = 761)	SD
Age (yr)	73*	7	70	7	73*	7	71	7
Systolic blood pressure (mm Hg)	144†	19	139	20	143	20	139	23
HDL cholesterol (mg/100 ml)	49†	19	46	13	57	15	59	16
LDL cholesterol (mg/100 ml)	144	37	142	37	157	36	155	40
Cigarette use (%)	15	. . .	25	. . .	23	. . .	28	. . .
Blood sugar (mg/100 ml)	119	33	113	31	113‡	27	109	26
Quetelet's index (kg/m^2)	29‡	4	27	3	27*	4	26	4

Cases significantly different from noncases: * $p < 0.001$; † $p < 0.05$; ‡ $p < 0.0001$.
HDL = high density lipoprotein; LDL = low density lipoprotein; SD = standard deviation.

TABLE II Cardiovascular Risk Factors in Framingham Offspring Study Subjects With and Without Extra Echocardiographic Spaces

	Male Subjects				Female Subjects			
Variable	Average Cases (n = 37)	SD	Average Noncases (n = 1,509)	SD	Average Cases (n = 57)	SD	Average Noncases (n = 1,595)	SD
Age (yr)	53*	8	44	10	53*	7	43	10
Systolic blood pressure (mm Hg)	137†	18	122	18	131†	22	117	19
HDL cholesterol (mg/100 ml)	44	11	44	11	59	17	57	15
LDL cholesterol (mg/100 ml)	143‡	35	130	35	134*	34	118	33
Cigarette use (%)	32	. . .	42	. . .	30	. . .	42	. . .
Blood sugar (mg/100 ml)	116†	41	104	12	101	11	98	11
Quetelet's index (kg/m^2)	28*	3	27	4	26*	4	24	4

Cases significantly different from noncases: * $p < 0.002$; † $p < 0.0001$; ‡ $p < 0.03$.
Abbreviations as in Table I.

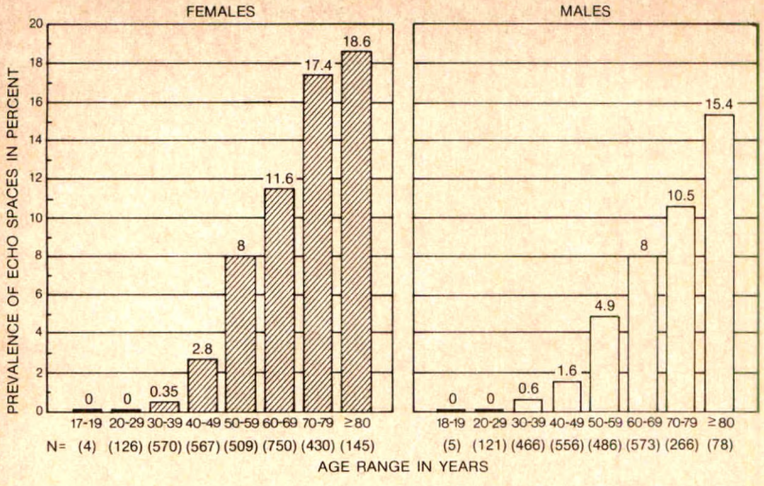

FIGURE 2. Relation of prevalence of posterior extra echocardiographic spaces to age in Framingham subjects.

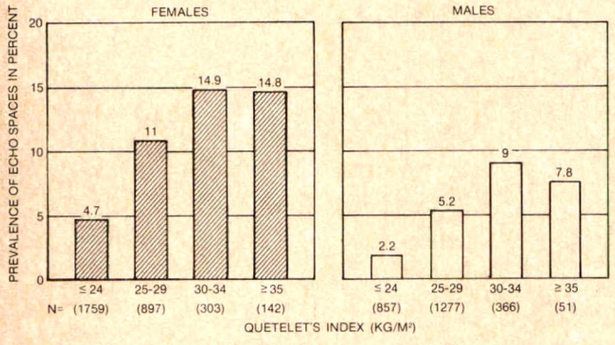

FIGURE 3. Relation of posterior extra echocardiographic spaces to Quetelet's index in Framingham subjects.

ranged from <1% in subjects in the 20- to 30-year age decade to more than 15% for those in their 80s. Figure 2 summarizes the prevalence of these spaces in Framingham Study subjects. The extra echocardiographic spaces were categorized as possible in 198 (56%) of the 370 subjects with such spaces. Only 18 of the subjects (9 male, 9 female; mean age 68 ± 12 years) had extra echocardiographic spaces of moderate size. Only 30 (1.2%) of 2,411 subjects under age 50 years had extra echocardiographic spaces. The spaces in subjects under age 50 were invariably <10 mm.

With some exceptions, extra echocardiographic spaces tended to be more common in subjects who were older, female, obese, and more hypertensive and who had higher blood sugar and higher low density lipoprotein cholesterol levels (Tables I and II). Among these cardiovascular risk factors, obesity and age were significantly and independently associated with such echocardiographic spaces in multivariate analysis (Fig. 2 and 3, Tables III and IV). In Offspring Study female subjects, only age was significantly and independently associated with extra echocardiographic spaces (Table IV). High density lipoprotein cholesterol was significantly and independently associated with the echocardiographically poor spaces in elderly men. No overt cardiac disease was found in 241 (65%) of the 370 subjects with extra echocardiographic spaces. Overt cardiac disease was no more common in those with than in those without possible or small extra echocardiographic spaces in age- and sex-specific comparisons. Thirteen (72%) of the 18 subjects with moderate-sized spaces had overt cardiac disease. This figure was nearly twice the prevalence of overt cardiac disease found in those of similar age and sex without extra echocardiographic spaces. A variety of cardiac diseases were found in the 13 subjects, including hypertensive heart disease (7), valvular heart disease (3), coronary heart disease (2), and hypertrophic cardiomyopathy (1). Two subjects with hypertensive heart disease also had symptoms suggesting congestive failure. One subject with moderate effusion had an apparently thickened pericardium (Fig. 1, bottom), but no significant symptoms.

Hypertrophy of the interventricular septum or increased left ventricular mass was the only echocardiographic finding in cohort subjects that was consistently and significantly associated with such spaces in both sexes using age- and body size-adjusted comparisons. Interventricular septal hypertrophy was more than twice as likely in those with (32 of 194) than in those without (101 of 1,370) extra echocardiographic spaces ($p < 0.0001$). Echocardiographic left ventricular hypertrophy was significantly more likely in male Offspring Study subjects with than without extra echocardiographic spaces. Atrial fibrillation was 3 times more likely in cohort subjects with (13 of 215) than without (44 of 1,828) extra echocardiographic spaces ($p < 0.02$).

Discussion

The present study indicates a striking increase in the prevalence of posterior extra echocardiographic spaces with increasing age. The variance in prevalence estimates of extra echocardiographic spaces from clinical studies is undoubtedly partially explained by age differences and selective bias in the study groups. Data from the present study indicate that posterior extra echocardiographic spaces are common after age 60, with prevalences reaching 10 to 20%, whereas they are uncommon (prevalence about 1%) in subjects under age

TABLE III Multivariate Logistic Regression Coefficients of Cardiovascular Risk Factors of Framingham Cohort Study Subjects With and Without Extra Echocardiographic Spaces

Variable	Regression Coefficients	
	Male Subjects (n = 619)	Female Subjects (n = 894)
Age (yr)	0.50*	0.33†
Systolic blood pressure (mm Hg)	0.03	−0.01
HDL cholesterol (mg/100 ml)	0.31†	−0.04
LDL cholesterol (mg/100 ml)	0.01	−0.01
Cigarette use	−0.12	0.04
Blood sugar (mg/100 ml)	0.06	0.04
Quetelet's index (kg/m^2)	0.64‡	0.28†

* $p < 0.001$; † $p < 0.02$; ‡ $p < 0.0001$.
Abbreviations as in Table I.

TABLE IV Multivariate Logistic Regression Coefficients of Cardiovascular Risk Factors of Framingham Offspring Study Subjects With and Without Extra Echocardiographic Spaces

Variable	Regression Coefficients	
	Male Subjects (n = 1,546)	Female Subjects (n = 1,652)
Age (yr)	0.85*	0.86*
Systolic blood pressure (mm Hg)	0.25	0.21
HDL cholesterol (mg/100 ml)	0.04	−0.05
LDL cholesterol (mg/100 ml)	0.11	0.11
Cigarette use	−0.06	−0.18
Blood sugar (mg/100 ml)	0.15	−0.16
Quetelet's index (kg/m^2)	0.34†	0.17

* $p < 0.0001$; † $p < 0.05$.
Abbreviations as in Table I.

50. In this free-living general population these spaces were usually small, with only 18 (0.3%) of the study group having moderate-sized spaces.

Berger et al[4] found moderate (>10 mm) or large (>20 mm) spaces in almost half the 171 patients they studied with extra echocardiographic spaces. Of their subjects, 95% had overt cardiac or systemic disease. In another clinical series, Riba and Morganroth[19] found overt cardiac disease in 41 (60%) of 68 patients who had clinically unsuspected extra echocardiographic spaces. They found extra echocardiographic spaces frequently in the setting of congestive heart failure. Rare causes of extra echocardiographic spaces have included pericardial neoplasm, coronary artery aneurysm, fistula, posterior thoracic aorta, left ventricular pseudoaneurysm, mitral anular calcification, and pleural effusion.[27–30] Subjects in the present study with possible or small areas usually had no overt cardiac disease, whereas subjects with moderate-sized spaces usually had overt cardiac disease. Only 1 subject with moderate-sized spaces had overt congestive heart failure.

Anterior extra echocardiographic spaces in the absence of posterior spaces were usually considered to represent epicardial fat.[2,3] Recent computerized tomography correlations with echocardiography confirm this impression.[31] Computerized tomographic study of 50 patients who had posterior extra echocardiographic spaces disclosed subepicardial fat both anteriorly and posteriorly in 18 patients.[32] The posterior spaces had an echocardiographic appearance indistinguishable from that of pericardial fluid.

Obesity is associated with increased subepicardial fat. Although such fat is more common and found in greater amounts anteriorly, appreciable aggregations of fat may be found posterior to the left ventricular free wall. Autopsy data indicate that subepicardial fat increases with age.[33] The strong relation of obesity and increased age to the presence of posterior extra echocardiographic spaces in the present study is consistent with the hypothesis that many spaces represent subepicardial fat with or without small amounts of (perhaps physiologic) pericardial fluid. The lack of overt evidence of cardiac disease in most subjects in the present study gives additional support to this hypothesis.

Obesity, hypertension, and ventricular septal hypertrophy are related and suggest another mechanism favoring fluid as an explanation for extra echocardiographic spaces. Pericardial fluid could be a marker for subclinical congestive heart failure in hypertensive patients with ventricular hypertrophy. The relatively poor cardiovascular risk factor profile in subjects with extra echocardiographic spaces is compatible with this possibility. Hypertensive hypertrophy is also a prominent precursor to atrial fibrillation.[34] However, in the cohort, the correlation of echocardiographic spaces with obesity was more impressive than that with interventricular septal hypertrophy. Furthermore, when ventricular septal hypertrophy was included in the multivariate analysis the obesity-echocardiographic space relation persisted.

The association of atrial fibrillation with extra echocardiographic spaces in the present study is consistent with the known association of atrial dysrhythmias with pericardial disease. However, Isner et al[35] have described computerized tomographic evidence of accumulations of fat in the interatrial septae in obese patients. Whether this might be associated with extra echocardiographic spaces (secondary to subepicardial fat) and lead to atrial dysrhythmias deserves investigation. Whether the lack of a significant relation of extra echocardiographic spaces to obesity in the younger Offspring Study female subjects indicates a different pathogenesis compared with that in male and older subjects is unclear but also deserves investigation. The association of high density liproprotein cholesterol with extra echocardiographic spaces in elderly men is not easily explained.

In any event, recognition that posterior extra echocardiographic spaces may in some cases represent subepicardial fat is important because it could help

avoid labeling subjects with nonspecific symptoms as having pericarditis. The possibility of alternative explanations for such spaces deserves further study. Such study should include evaluation of the specificity of various echocardiographic findings as indicators of fluid. In the meantime, computerized tomography may be useful in confirming the presence of pericardial fluid. This is appropriate when fluid and fat must be distinguished (for example, contemplated pericardiocentesis) in the presence of any doubt about the echocardiographic findings.

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Effect of Verapamil on Left Ventricular Function: A Randomized, Placebo-Controlled Study

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Verapamil has a negative inotropic action in isolated cardiac muscle. Its effects on left ventricular function were tested in 25 patients with suspected coronary artery disease. A double-blind, randomized, placebo-controlled study design was used. Verapamil (0.2 mg/kg over 10 minutes) significantly lowered mean arterial pressure (from 105 to 89 mm Hg) while increasing the cardiac index (from 2.8 to 3.1 liters/min/m^2). No statistically significant effect was seen on heart rate, left ventricular end-diastolic pressure or end-systolic volume index, ejection fraction, peak rates of systolic wall thickening or diastolic wall thinning, or percentage of hemiaxial shortening. However, there was a small increase in the left ventricular end-diastolic volume index (from 94 to 102 ml/m^2). Important findings were a reduction in systemic vascular resistance (from 39 to 30 U·m^2), an increase in left ventricular end-diastolic volume index consistent with a negative inotropic effect, and no evidence of improved regional wall dynamics in portions of the left ventricular wall considered hypokinetic because of myocardial ischemia.

The calcium channel-blocking drug verapamil has clinically important cardiovascular effects. Its slow-channel inhibition in vascular smooth muscle and myocardium produces systemic and coronary vasodilatation and depression of sinoatrial and atrioventricular nodal function.[1] Recognition of these properties has led to its successful use in chronic angina pectoris,[2,3] coronary artery spasm,[4,5] and supraventricular tachycardias.[6,7]

In vitro studies show, however, that verapamil depresses myocardial contractility.[8,9] Some impairment in myocardial function has also been noted in open-label patient studies performed in the cardiac laboratory.[10,11] Available evidence suggests that this in vivo effect is chiefly seen in patients who have markedly impaired ventricular function.

We thus sought to examine the effects of verapamil on global and regional left ventricular function in patients with suspected coronary artery disease but without evidence of heart failure. We wished to test for adverse effects of the drug on indexes of left ventricular function in such patients, and, in addition, to test the hypothesis that regional wall dynamics in areas of myocardium presumed to be ischemic improve after administration of verapamil.

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Methods

Serial measurements of cardiac function made in the catheterization laboratory are known to be subject to many sources of variation.[12] To minimize the biases these and other variations would introduce, we used a randomized, double-blind, placebo-controlled study design.

Selection of patients: The patients selected had been referred to the cardiac laboratory for coronary arteriography because of suspected coronary artery disease, usually on the basis of the presence of angina pectoris. They had no evidence of other heart disease, and there were no clinical signs of heart failure. Study patients were not taking other cardioactive medications. Specifically, no beta-adrenergic blockers had been administered during the 48 hours before the study and no nitrates had been given within 12 hours. The investigation was approved by the Mayo Clinic Human Studies Committee. It was discussed with each patient, and informed consent was obtained.

Study protocol: The study was performed before coronary arteriography and utilized a fluid-filled catheter in the left ventricle and a cannula in the left brachial artery. Baseline measurements were obtained of arterial pressure, heart rate, left ventricular end-diastolic pressure, and cardiac output as determined from an indocyanine green dye curve, with in-

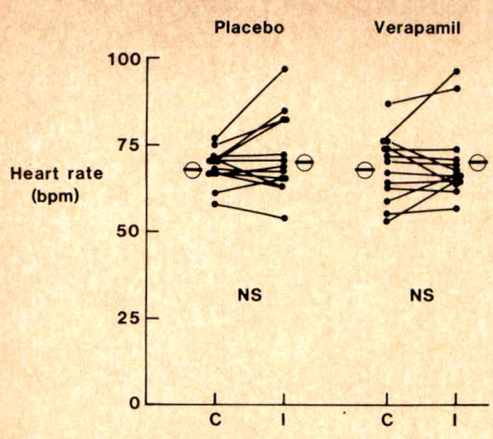

FIGURE 1. Control (C) and postintervention (I) values for heart rate in placebo and verapamil treatment groups. Differences are not significant (NS). The **larger circles** represent mean values. bpm = beats per minute.

TABLE I Effects of Verapamil on Left Ventricular Function: Results of Randomization (Mean Baseline Values)

Variable	Placebo (12 Patients)	Verapamil (13 Patients)*
Age (yr)	55	55
Vessels diseased (n)	2.1	2.0
Heart rate (beats/min)	68	68
Mean arterial pressure (mm Hg)	103	105
Cardiac index (liters/min/m^2)	2.9	2.8
Left ventricular end-diastolic pressure (mm Hg)	17	16
Left ventricular end-diastolic volume index (ml/m^2)	91	94
Left ventricular end-systolic volume index (ml/m^2)	37	39
Ejection fraction (%)	60	58

* Ventriculographic data available for only 9 patients.

jection of dye into the left ventricle and brachial artery sampling. A biplane left ventricular videoangiogram was obtained after injecting 0.5 ml/kg of Renografin®-76 over 3 seconds. After the patient had rested 5 minutes, a bolus intravenous injection of 0.1 mg/kg of verapamil or placebo was given. This was followed by a 10-minute infusion of 0.01 mg/kg/min, for a total dose of 0.2 mg/kg. At the end of the infusion, repeat measurements were made of arterial pressure, heart rate, left ventricular end-diastolic pressure, and cardiac index, and another left ventricular videoangiogram was obtained.

Analysis of ventriculograms: The left ventriculograms were analyzed by biplane roentgen videometry interfaced with a CDC 3500 computer, as previously described.[13,14] Bright outlines are automatically generated by a videoquantizer to identify the endocardial and epicardial borders for computer analysis. Ventricular volumes and ejection fraction are determined from the endocardial outlines with use of a volume-computing program based on Simpson's rule. Peak rates of regional myocardial thickening and thinning are computed from 60-per-second measurements of the ventricular wall thickness, defined as the shortest distance between the endocardium and the epicardium. In this study, the peak rates were determined from a single segment of the anterolateral wall, approximately midway between the apex and the base of the heart. The advantages and limitations of this method of assessing regional myocardial function have been discussed previously.[14,15]

Regional contraction was also assessed from measurements of hemiaxial shortening. The measurements were obtained by manually superimposing end-diastolic and end-systolic left ventricular silhouettes, the diaphragm and ribs being used as fixed reference points. The silhouettes were then rotated onto a common midaortic valve-to-apex axis, and 3 equidistant cords were drawn to yield 6 hemiaxes.[11]

Coronary arteriography was performed by standard techniques, and angled views were routinely obtained. The degree of coronary arterial narrowing was judged subjectively and was expressed as the mean percentage of reduction in luminal diameter of the coronary artery from multiple views. Routine 12-lead electrocardiograms and vectorcardiograms were reviewed for evidence of transmural myocardial infarction.

Statistical analysis: The randomization code was broken only after all patient studies and measurements had been completed. The significance of differences obtained between control and intervention values was tested by Student's paired *t* test.

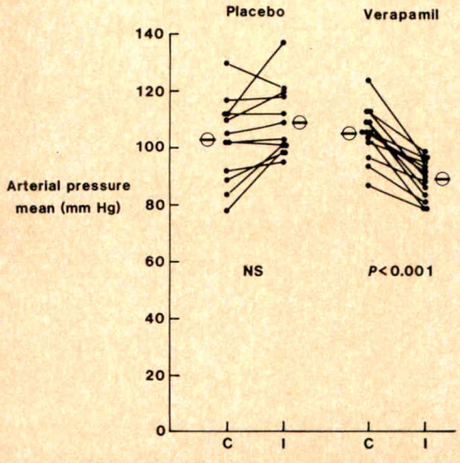

FIGURE 2. Mean arterial pressure values in placebo and verapamil groups before (C) and after (I) intervention. The verapamil group showed a highly significant decrease ($p < 0.001$).

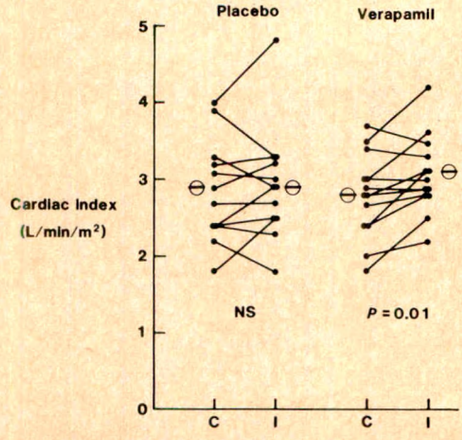

FIGURE 3. The values for cardiac index showed a small but significant increase ($p = 0.01$) when verapamil was the intervention. C = control; I = intervention; NS = not significant.

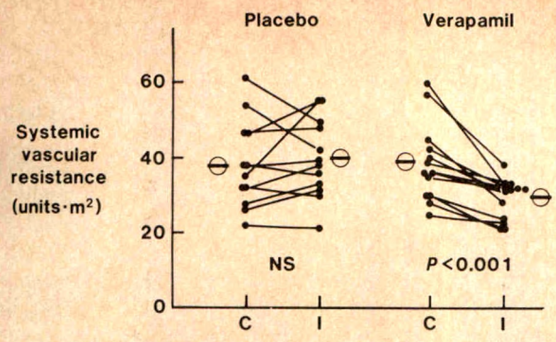

FIGURE 4. Systemic vascular resistance in placebo and verapamil treatment groups. C = control; I = intervention; NS = not significant.

Results

In all, 24 male patients and 1 female patient were entered into the study. Randomization resulted in allocation of 12 patients to the placebo group and 13 to the verapamil group. The 2 groups were similar in mean age and mean number of diseased vessels. The coronary arteriogram was normal in 1 patient in the placebo group and in 2 in the verapamil group. Mean baseline values were similar in the placebo and verapamil groups for heart rate, mean arterial pressure, cardiac index, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, and left ventricular ejection fraction (Table I).

Control values and those obtained after the placebo or verapamil intervention are shown in Figures 1 through 5. Some patients showed considerable variation in heart rate, but the mean values were only slightly altered after either intervention (Fig. 1).

Although the mean arterial pressure was no different overall before and after infusion of placebo, the response to infusion of verapamil was consistent and highly significant (Fig. 2). The mean arterial pressure decreased in every subject; the mean decrease was 15%. The cardiac index increased in 9 of the 13 patients treated with verapamil and no change occurred in the placebo group (Fig. 3).

With the decrease in mean arterial pressure and the increase in cardiac index, the calculated systemic vascular resistance showed a highly significant reduction in the verapamil treatment group (Fig. 4). Postinfusion values were lower in every case. No significant change was noted in the placebo group.

TABLE II Effects of Verapamil on Left Ventricular Function: Response of Selected Variables

Variable	Placebo (12 Patients)		Verapamil (13 Patients)*	
	Before	After	Before	After
Left ventricular end-diastolic pressure (mm Hg)	17	19	16	19
Left ventricular end-systolic volume index (ml/m²)	37	34	39	41
Ejection fraction (%)	60	62	58	59

* Ventriculographic data available for only 9 patients.

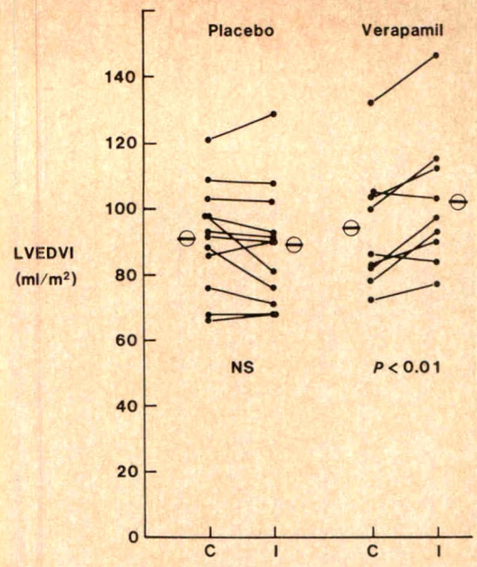

FIGURE 5. Left ventricular end-diastolic volume index (LVEDVI) in the 2 treatment groups. A significant increase was seen in the patients treated with verapamil ($p < 0.01$). C = control; I = intervention; NS = not significant.

A significant difference was found in the left ventricular end-diastolic volume index in patients after verapamil infusion but not in the placebo group. It increased in 7 of the 9 patients treated with verapamil in whom it could be calculated—from a mean of 94 to 102 ml/m² (Fig. 5). In 4 patients treated with verapamil, premature ventricular contractions rendered 1 of their ventriculograms unsuitable for analysis.

No significant response was detected after placebo or verapamil administration for left ventricular end-diastolic pressure, left ventricular end-systolic volume index, or ejection fraction (Table II). A small increase seen in left ventricular end-diastolic pressure after verapamil did not achieve significance, nor could any increase in left ventricular end-diastolic pressure be related to the initial level (range 7 to 26 mm Hg).

Peak rates of systolic thickening and diastolic thinning of the anterolateral wall were essentially unchanged after verapamil and placebo administration

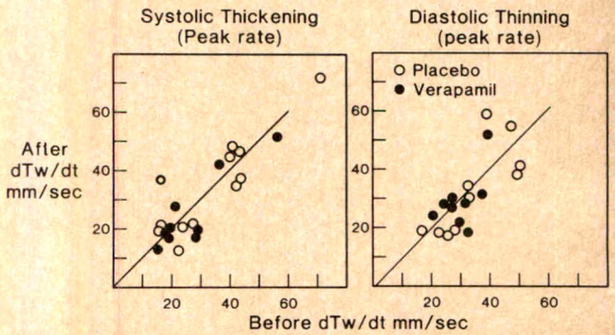

FIGURE 6. Maximal rate (dTw/dt) of systolic thickening and diastolic thinning for a single anterolateral left ventricular wall segment in placebo and verapamil treatment groups.

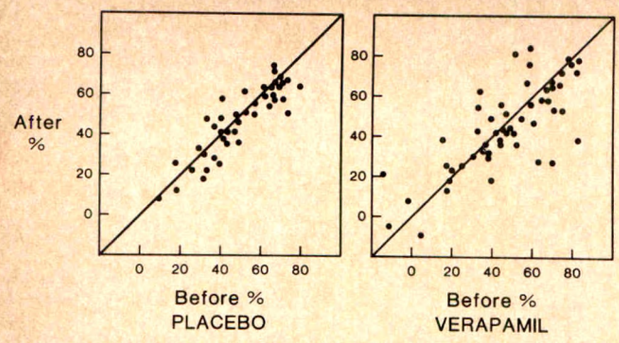

FIGURE 7. Hemiaxial shortening measured before and after the interventions with placebo and verapamil.

(Fig. 6). This was true not only for segments considered normal (dTw/dt ≥ 5.0 cm) but also for hypokinetic segments presumed ischemic, in which peak rates of systolic wall thickening were between 0 and 5.0 cm/s. In assessing such responses, it is necessary to evaluate the severity of the obstructive disease in the artery supplying the segment and the underlying state of the myocardium in that area.

In the placebo group, of 11 segments showing systolic hypokinesia, 6 were supplied by an artery with significant (that is, ≥50% stenosis) obstruction, and none of these had electrocardiographic evidence of anterior myocardial infarction. Of eight systolic hypokinetic segments in the verapamil group, 4 were supplied by an artery with significant obstruction, and 1 had electrocardiographic evidence of anterior myocardial infarction.

A total of 96 segments were suitable for analysis of hemiaxial shortening, both before and after infusion. Usually, 4 to 6 hemiaxes in each patient were suitable for this comparison. Poor endocardial opacification, especially in the left ventricular inflow region, led to the rejection of some segments from consideration. Although the verapamil group demonstrated greater variation in the values before and after intervention, there was no greater trend to either improvement or deterioration (Fig. 7).

Discussion

In patients with suspected coronary artery disease who do not have overt heart failure, verapamil lowers systemic vascular resistance, as evidenced by a decrease in arterial pressure and an increase in cardiac index. In this setting, the small but significant increase in the end-diastolic volume index observed seems most likely to represent a negative inotropic effect of verapamil, necessitating a larger end-diastolic volume to accomplish the increase in cardiac index associated with peripheral vasodilatation. This finding is consistent with the previously reported negative inotropic effects of verapamil in isolated cardiac muscle.[8,9] However, the possibility of a change in diastolic compliance of the ventricle cannot be excluded. The present findings differ from those of Ferlinz et al,[11] who reported an increase in left ventricular ejection fraction and circumferential fiber shortening, which they interpreted as improvement in left ventricular function with the use of verapamil. It should be noted that the quantitative indexes of left ventricular function reported by Ferlinz et al were determined from single-plane left ventriculograms by use of the area-length method, an approach with significant limitations in patients with coronary artery disease and regional left ventricular function abnormalities.[16]

The apparent negative inotropic effect observed in our study after a large intravenous dose of verapamil was unassociated with any changes that would be clinically evident. However, it provides support for caution in the use of the drug in patients with borderline compensation of left ventricular function, particularly in the presence of myocardial ischemia.

The studies reported here raise a number of questions relating to the mechanisms by which verapamil may provide relief of angina pectoris. Several possible mechanisms appear to exist, all of which could be operative to varying degrees, depending on the individual patient. The potent peripheral vasodilating effect of verapamil documented in the present study by a consistent decrease in arterial pressure, as well as by other evidence of both arterial and venous dilatation,[17] should produce a reduction in cardiac work and myocardial oxygen demands. These changes are not associated with reflex tachycardia, apparently because of the depressant effect of verapamil on pacemaker and conduction tissue[18]; thus, an additional stimulus for increased oxygen demand is avoided.

Another possible mechanism for relief of angina with verapamil is an increase in blood flow to the ischemic area through collateral channels and direct vasodilatation of the atherosclerotic segment of the coronary artery. Verapamil has been demonstrated to have a potent vasodilating effect in extramural coronary arteries.[19] That vasodilating agents may have a major effect on improving flow, even through so-called fixed coronary arteries, receives strong support from the recent work of Brown et al[20] on the effect of nitroglycerin on such lesions, in which a computer-based quantitative method was used to determine changes in the degree of obstruction. Although several studies have shown no change in the rate-pressure product for angina after verapamil treatment,[21,22] data are reported on patients with stable angina which indicate that another calcium-channel blocker, lidoflazine, improves regional perfusion of ischemic myocardium during exercise.[22]

The lack of improvement in regional function of hypokinetic areas after administration of verapamil in the present study raises the question of local reduction of myocardial oxygen demands. There are data to support the use of rates of wall thickening and thinning as indexes of myocardial ischemia in animal models[23] (St. John Sutton M, Ritman EL: unpublished data). Thus, if an intervention relieves ischemia, one would expect an improvement in such areas if the muscle is still viable and the intervention produces no inotropic effect. This is the case in the studies reported by Dumesnil et al[14] and Chesebro et al,[15] in which the intervention is with nitroglycerin. However, with verapamil, an agent known to have negative inotropic effects, a different response

occurs. In spite of peripheral and central effects, which result in decreased oxygen demand and perhaps increased regional blood flow, no regional improvement in function occurs. Previous studies have suggested that ischemic areas of myocardium may, in fact, be most susceptible to the negative inotropic effects of verapamil, in contrast to propranolol, which affects both normal and ischemic tissue by depressing function.[24] Such negative inotropic effects in a local area of myocardial ischemia might contribute to relief of angina pectoris, not only on the basis of decreased myocardial oxygen demands but also through facilitation of local flow, as demonstrated by Marzilli et al.[25]

The observations in our study on regional wall dynamics differ from those reported by Ferlinz et al,[11] who used the measurement of hemiaxes as an index of regional function. That investigation reported frequent improvement with verapamil therapy, but no control group was included. In our study, the use of a placebo-controlled design helps resolve this difference, in that changes similar to those in the verapamil group could be observed in the placebo group as well. This reflects the limitations of the hemiaxial method in assessing regional function, because the identification of axes is highly subjective and is influenced by cardiac motion.

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Hemodynamic and Electrocardiographic Effects in Man Of a New Nonionic Contrast Agent (Iohexol): Advantages Over Standard Ionic Agents

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Iohexol is a new, nonionic contrast material that has been shown in animal studies to hold great promise as an agent for coronary arteriography and ventriculography with fewer adverse hemodynamic effects than standard ionic media. At present, it has not been studied systematically in man. Fifty patients referred for elective cardiac catheterization were randomized to receive either iohexol or meglumine sodium diatrizoate (Renografin®-76). Both operator and patient were blinded as to which agent was being used. Hemodynamic variables measured were pulmonary artery wedge pressure and systemic blood pressure. In addition, the following electrocardiographic indexes were evaluated: S-T segment shifts, changes in Q-T interval, changes in T-wave amplitude, and changes in heart rate. These variables were measured after left ventriculography and after both left and right coronary arteriography. Both iohexol and sodium meglumine diatrizoate produced small transient elevations in pulmonary artery wedge pressure. Systemic hypotension occurred with both agents but was more profound and longer-lasting with sodium meglumine diatrizoate. Iohexol injection resulted in no electrocardiographic changes, whereas sodium meglumine diatrizoate produced marked Q-T prolongation, as well as changes in T-wave amplitude and heart rate. Iohexol was well tolerated by the patients, and radiographic opacification was good to excellent in all cases. Thus, iohexol produces fewer deleterious hemodynamic and electrocardiographic changes than sodium meglumine diatrizoate when studied in a typical adult population requiring diagnostic cardiac catheterization. This favorable preliminary experience in man has potential widespread importance because of the large number of patients undergoing angiographic procedures.

The deleterious effects of ionic contrast material on myocardial function during coronary arteriography and contrast ventriculography have long been appreciated.[1–8] These effects include a reduction in left ventricular peak systolic pressure and both global and regional myocardial function, as well as adverse electrophysiologic changes. These perturbations occur more frequently in the presence of coronary stenoses.[8,9] Important etiologic factors in the generation of these phenomena include excessive amounts of single-valence cations such as sodium and meglumine in the media, contrast-induced hypocalcemia and hypokalemia, and the osmolality of these solutions.[1,2,6,10–18] Sodium meglumine diatrizoate (Renografin®-76) has frequently been shown to produce these adverse cardiovascular effects, and at present is the most commonly used angiographic contrast medium. Efforts to develop nonionic contrast agents devoid of these toxic properties have been pursued. Such an agent would be expected to be safer for general patient use and would interfere less with the ability of the clinical cardiologist to interpret physiologic data from angiographic data. Metrizamide (Amipaque®) was the first generally available nonionic contrast agent to demonstrate some of these advantages; however, its expense and hydrolytic instability make it less than ideal for routine clinical use.

Iohexol is a new, nonionic contrast material which has a long shelf life in solution and is hydrolytically stable. Although extensive research in laboratory animals has shown that iohexol causes less severe hemodynamic[9] and electrocardiographic alterations[17] than standard ionic contrast media, a systematic comparison of iohexol and sodium meglumine diatrizoate during coronary

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TABLE I Characteristics of Patient Groups

	Group 1 (R76 n = 25)	Group 2 (Iohexol, n = 25)
Age (yr)	58 ± 9	61 ± 6
Coronary artery disease (patients [n])		
1 Vessel	2	5
2 Vessels	9	5
3 Vessels	9	9
Valvular disease (patients [n])		
Mild to moderate mitral regurgitation	1	5
Mild to moderate aortic regurgitation	1	2
Ejection fraction (%)	62 ± 17	62 ± 14
Left ventricular end-diastolic volume index (ml/m^2)	80 ± 26	82 ± 36
Volume of contrast injected (ml)		
Left ventriculography	41 ± 3	40 ± 7
Left coronary arteriography	6 ± 1	6 ± 1
Right coronary arteriography	5 ± 2	5 ± 2
Concomitant medications (patients [n])		
Digitalis glycosides	9	8
Nitrates	21	19
Beta-blocking agents	19	17
Calcium antagonists	11	8
Antiarrhythmic agents	4	4

R76 = Renografin-76 (sodium meglumine diatrizoate).

arteriography and left ventriculography in man has not been undertaken. This study was designed to investigate the hemodynamic and electrocardiographic differences between iohexol and sodium meglumine diatrizoate during elective cardiac catheterization in adult patients.

Methods

All patients referred for elective cardiac catheterization were eligible for this study except (1) patients with a serum creatinine level >3.0 mg/100 ml; (2) those with a known sensitivity to iodine; (3) pregnant or lactating women; and (4) patients who had received contrast media within 48 hours of the study. The patients and the angiographer were blinded as to which contrast agent was being utilized. The study was terminated when 50 patients (25 in each group) had been randomized to receive either sodium meglumine diatrizoate or iohexol. Pertinent clinical features of these 2 groups are shown in Table I. The 2 groups were composed of patients with similar clinical and angiographic findings (no significant differences with chi-square analysis).

Patients were studied by either the Sones or Judkins techniques after premedication with oral diazepam, 5 to 10 mg, and diphenhydramine, 25 to 50 mg. A Potts-Cournand needle was inserted into the left brachial artery for continuous monitoring of systemic pressure. A #7 French flotation catheter was advanced into the pulmonary artery wedge position.

Variables were analyzed for 2 minutes after left ventriculography and for 1 minute after each of the first left and right coronary artery injections: The variables were measured during a preinjection control period, at 5-second intervals for 20 seconds after dye injection, and at 10-second intervals thereafter. Left ventricular injection was performed during held inspiration whereas the first selective injection into each coronary artery was performed during quiet respiration. An interval of approximately 15 minutes elapsed between left ventriculography and coronary arteriography. The amount of dye used for each injection was recorded and is shown in Table I.

The hemodynamic variables of interest were the systemic systolic arterial pressure and the pulmonary wedge pressure. The S-T segment shifts, Q-T interval, T-wave amplitude, and heart rate were also measured from limb lead II of the electrocardiogram. All recordings were made at a strip chart speed of 100 mm/s.

The protocol was approved by the Human Subjects Investigation Committee of the University of California, San Diego; all patients gave informed consent.

Statistics: All data were analyzed by repeated analysis of variance to test for (1) changes induced by each agent over time, (2) differences between the effects of each agent at specific points in time, and (3) differences in the overall time course of changes between the contrast media. Differences were considered significant if p was <0.05. Tabular data are presented as mean ±1 standard deviation whereas the data in graphs represent mean ±1 standard error of the mean.

Results

The preinjection control values are provided in Table II. No statistical difference at control was noted between the groups except for the systemic systolic pressure before left ventriculography, which was significantly higher for the iohexol group ($p < 0.05$). Data are therefore presented in raw form in order to not exaggerate differences between the agents when percent changes are analyzed.

Hemodynamic effects: Figure 1 summarizes the results of these measurements for both groups. The sequence of changes in pulmonary wedge pressure was the same for the sodium meglumine diatrizoate group

TABLE II Control Values

	Left Coronary Injection		Right Coronary Injection		Left Ventriculography	
	R76	Iohexol	R76	Iohexol	R76	Iohexol
Pulmonary wedge pressure (mm Hg)	8 ± 10	10 ± 6	8 ± 4	10 ± 5	9 ± 4	11 ± 8
Systemic systolic pressure (mm Hg)	135 ± 20	148 ± 28	132 ± 20	144 ± 26	133 ± 19	152 ± 25*
S-T segment (mV)	−0.02 ± 0.10	−0.06 ± 0.08	−0.02 ± 0.11	−0.09 ± 0.21	−0.03 ± 0.10	−0.05 ± 0.08
Q-T interval (ms)	434 ± 52	420 ± 57	430 ± 59	428 ± 54	431 ± 51	424 ± 51
T-wave amplitude (mV)	0.17 ± 0.16	0.14 ± 0.21	0.18 ± 0.14	0.16 ± 0.19	0.19 ± 0.13	0.12 ± 0.17
Heart rate (beats/min)	64 ± 11	69 ± 19	65 ± 12	69 ± 19	64 ± 10	69 ±17

* $p < 0.05$ versus sodium meglumine diatrizoate.
R76 = Renografin-76 (sodium meglumine diatrizoate).

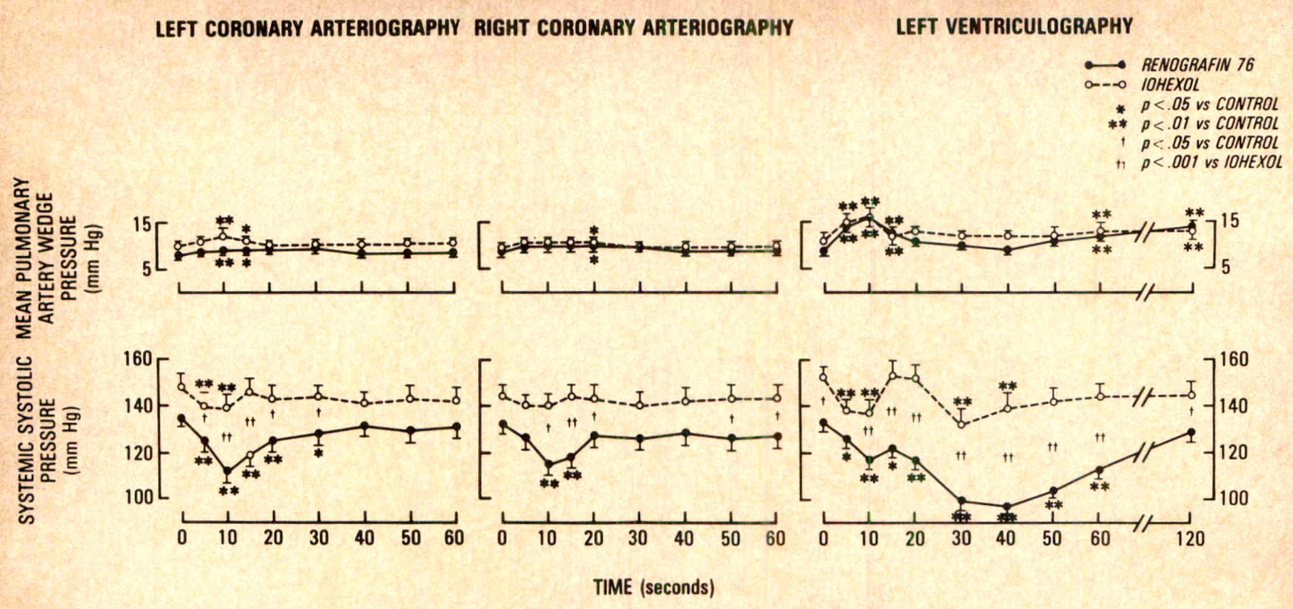

FIGURE 1. Hemodynamic changes induced by contrast agents.

and the iohexol group. While both agents induced small but statistically significant elevations in the mean pulmonary artery wedge pressure, there were no differences in the degree of this change between the 2 forms of media. In contrast, the time course of changes in systolic pressure induced by iohexol was significantly different from those induced by sodium meglumine diatrizoate after left and right coronary arteriography ($p < 0.05$) and after left ventriculography ($p < 0.001$), and in all 3 instances, the curves were flatter for iohexol and varied from control for shorter periods than the sodium meglumine diatrizoate group. Iohexol induced no blood pressure change after right coronary arteriography. After left coronary arteriography and left ventriculography, both agents produced significant decreases in pressure, but in both cases the decreases were smaller and less sustained after iohexol than after sodium meglumine diatrizoate. Furthermore, although the control blood pressure before left ventriculography was higher in the iohexol group, the trend analysis confirmed a significantly greater and longer lasting blood pressure decrease with sodium meglumine diatrizoate than with iohexol ($p < 0.001$).

Electrocardiographic effects: Figure 2 summarizes the results of the electrocardiographic measurements for both groups.

The S-T segment did not change significantly over time for either agent. Iohexol induced no changes in Q-T interval, T-wave amplitude, or heart rate. In marked contrast, sodium meglumine diatrizoate produced a substantial increase in the Q-T interval after left and right coronary arteriography and an increase in T-wave amplitude after left coronary arteriography. Furthermore, the heart rate was significantly depressed after coronary anteriography, and it increased significantly after left ventriculography performed with sodium meglumine diatrizoate.

Discussion

Iohexol is a new, nonionic, water-soluble contrast medium that has been shown to have great promise as a preferred agent for coronary arteriography and ventriculography in animal experimentation and in preliminary human studies. It does not dissociate in aqueous solution, contains negligible amounts of sodium, and the osmolality is approximately half that of ionic contrast agents (Table III). These properties provide a theoretical basis for the fewer hemodynamic and electrophysiologic effects of this agent as compared with ionic media. Furthermore, unlike metrizamide, a lyophilized nonionic substance which must be reconstituted before use, iohexol is premixed, stable in solution (even with autoclaving), and maintains its pH within a critical range for diagnostic angiography.

Animal studies have demonstrated fewer biochemical, electrocardiographic, and hemodynamic derangements induced by iohexol than by ionic contrast media.[9,19–28] Gerber et al[9] demonstrated significantly greater changes in left ventricular systolic pressure, first derivative of left ventricular pressure (dP/dt), dP/dt at 50 mm Hg developed pressure, end-systolic myocardial segment length (L), and first derivative of myocardial segment length (dL/dt) during sodium meglumine diatrizoate injection than with iohexol. They also noted that these effects were more marked in the ischemic state. Unlike sodium meglumine diatrizoate, iohexol does not cause any reductions in coronary sinus calcium or potassium levels and this may partially explain its fewer cardiodepressant effects.[9]

Higgins et al[28] demonstrated drastic biphasic changes in left ventricular pressure and dP/dt, and moderate changes in end-systolic dimension in response to the intravenous injection of sodium meglumine diatrizoate. In the same study, iohexol caused little or no change in

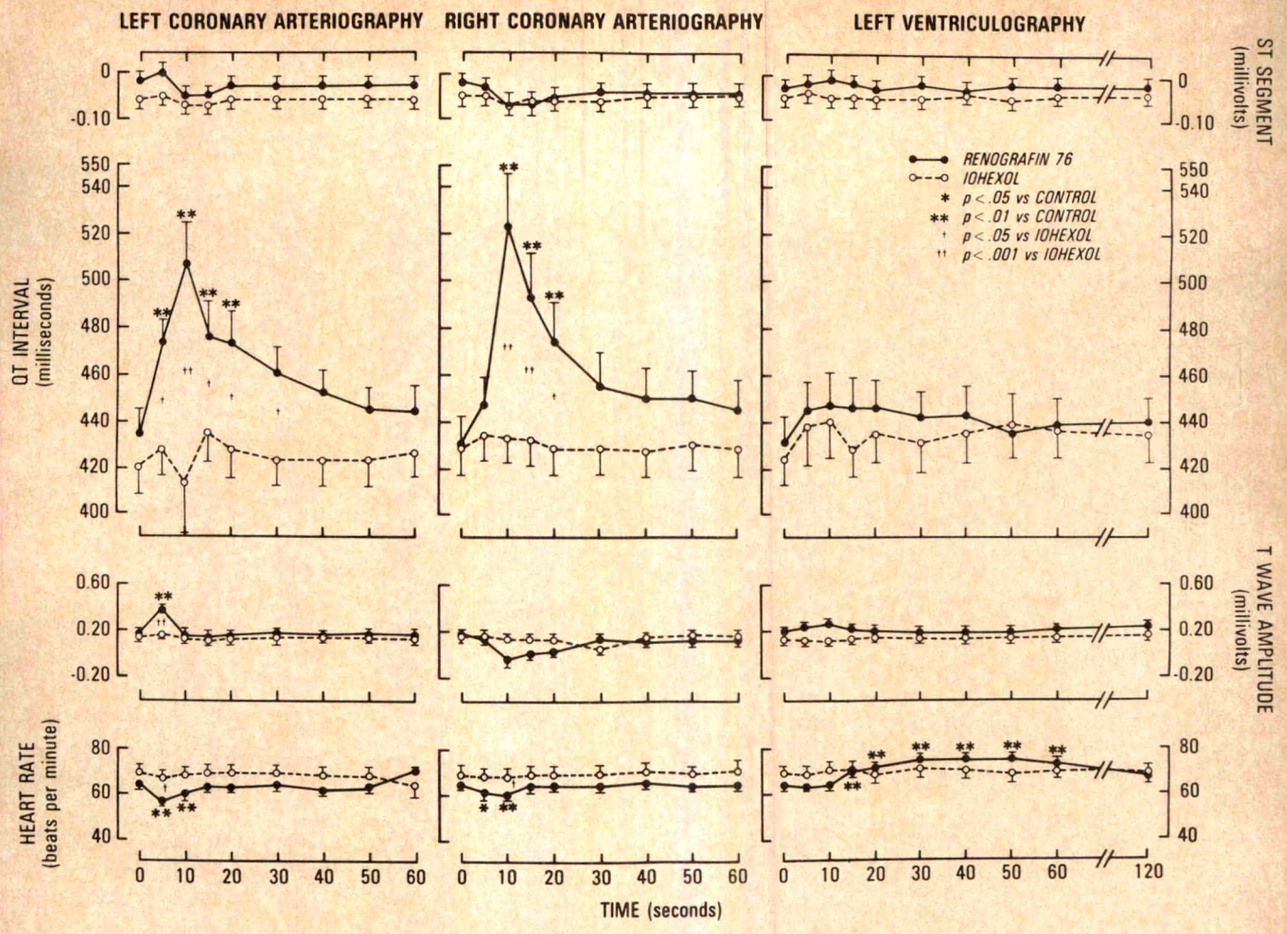

FIGURE 2. Electrocardiographic changes induced by contrast agents.

left ventricular pressure and dimensions. In addition, sodium meglumine diatrizoate caused marked arterial hypotension and large increases in coronary blood flow, while iohexol caused no significant changes in arterial pressure and coronary blood flow, and a mild increase in femoral blood flow. Based on these results, it was concluded that iohexol is preferable to standard ionic agents for deriving basic physiologic information from angiographic studies, including computed tomography and digital angiography.

Preliminary use of iohexol in humans has been reported by Aakhus et al.[29] This group demonstrated no significant heart rate, blood pressure, or electrocardiographic changes in 20 healthy volunteers who received 125 to 500 mgI/kg body weight of iohexol given intravenously. The injection was generally well tolerated, and a transient heat sensation was felt in only 6 of 10 patients who received the highest doses. This group also documented nearly complete renal excretion of unchanged iohexol within 24 hours of injection.

The present study reports our initial clinical experience with the use of iohexol for routine diagnostic cardiac catheterization. We found that iohexol produced a lesser degree of systemic hypotension after coronary angiography and left ventriculography. Furthermore, it induced no deleterious electrocardiographic changes as reflected by S-T segment shift, Q-T prolongation, changes in T-wave amplitude, or heart rate. The degree

TABLE III Physical Characteristics of Contrast Materials

	Iodine (mg/ml)	Osmolality (mOsmol/kg)	Viscosity Centipoise 20°	Viscosity Centipoise 37°C	Sodium (mEq/liter)	Calcium (mEq/liter)	Sodium Citrate mg/ml)	Disodium Edetate (mg/ml)
Sodium meglumine diatrizoate	370	1680	13.8	8.4	190	. . .	3.2	0.4
Iohexol	350	880	23.3	10.6	Negligible	Negligible	. . .	0.1*

* Calcium disodium edetate.

of opacification in all studies was also good to excellent and the agent was well tolerated by the patients.

We therefore conclude that iohexol has the potential benefit over ionic contrast material of producing fewer deleterious hemodynamic and electrocardiographic changes in patients undergoing diagnostic cardiac catheterization. These properties and the availability of the agent in a stable, premixed form with a long shelf life make it a practical and preferred contrast medium for routine clinical use. Such advantages are important for safer angiography, particularly in patients with coronary stenoses,[8,9] patients who are already hemodynamically unstable, and perhaps also for patients who suffer from arrhythmias. In addition, investigational studies using angiographic techniques should probably be carried out with an agent such as iohexol to avoid many of the physiologic derangements induced by standard ionic media.

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Increased Left Ventricular Function as an Adaptive Response in Vibration Disease

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Vibration disease results from the long-term use of vibrating tools. Vibration, noise, and cold are stressors that impair the human body, inducing vibration disease. From echocardiographic methods, the left ventricular ejection fraction in vibration disease was 79 ± 4%, a significantly higher value than that in control subjects (75 ± 6%) ($p < 0.01$). The increase in ejection fraction appeared to be due mainly to an increase in left ventricular end-diastolic dimension. The value of the ejection fraction was proportional to the activity of the autonomic nerves. The stroke volume index in patients with vibration disease was also significantly larger than that in the control subjects ($p < 0.001$). Electrocardiograms revealed a significantly lower heart rate at rest and an increase in the ratio of T waves to R waves in precordial lead V_6. These data suggest that the cardiovascular system in patients with vibration disease provides an adaptive response to the stressors.

Since 1911, long-term use of vibrating tools such as chain saws, pneumatic hammers, or electric hammers has been known to result in injury to peripheral blood vessels and nerves, giving rise to Raynaud's phenomenon in the fingers. This occupational disease has been called "white finger" or "vibration-induced white finger." [1] Recently, this condition has been recognized as a systemic disease. Long-term vibration impairs not only peripheral circulatory and nervous function, but also central nervous function.[2] The patients are afflicted with Raynaud's phenomenon and numbness of the fingers, insomnia, headache, palmar hyperhydrosis, fatiguability, tinnitus, and impotence.

The vibration and noise generated by vibration tools as well as the cold environment impair the human body.[2,3] Long-term exposure to these stressors could induce defense mechanisms in the human body. In particular, the sympathetic nervous system may become hyperreactive, and the adrenohypophyseal system may be excited.[4] Under these conditions, the cardiovascular system could adapt to the stressors. The patient would manifest signs and symptoms such as cardiomegaly, sinus bradycardia, and low blood pressure.[3] This study evaluates by echocardiography and electrocardiography the cardiovascular function of patients with vibration disease.

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Methods

The study group consisted of 35 men with vibration disease and a control group of 35 healthy men. All the subjects underwent physical and laboratory examination to exclude the possibility of cardiovascular or hormonal disease. All were physical laborers (farmers, firemen, railroadmen, carpenters, and industrial workers). The subjects of both groups were matched by age which ranged from 36 to 64 years. The average age in patients with vibration disease was 49 ± 7 years (mean ± standard deviation [SD]) and in the control group 48 ± 7 years. Chain saws and jack hammers were used by 20 and 15 men, respectively, for 16 ± 5 years (mean ± SD). The mean period between the last use of a vibrating tool and the examination was 3 ± 1.4 years (mean ± SD).

A standard M-mode echocardiogram was recorded in all subjects by 1 technician. The left ventricular ejection fraction was calculated from measurements of left ventricular end-diastolic and end-systolic dimensions in the echocardiogram, using the following formula: $(LVDd^3 - LVDs^3)/LVDd^3$, where LVDd = left ventricular end-diastolic dimension and LVDs = left ventricular end-systolic dimension.

Electrocardiograms (12 leads) were recorded in the supine position at a paper speed of 25 mm/min. The following variables were studied: heart rate calculated from the mean of 3 beats; the algebraic sum of Q, R, and S deflections in standard leads (R in lead I + S in lead III) and in precordial leads (S in lead V_1 + R in lead V_5); and the ratio of the amplitudes of T waves to those of R waves in leads I, V_5, and V_6. The activity

TABLE I Echocardiographic Measurements in Patients With Vibration Disease and Control Subjects

	Patients With Vibration Disease (n = 35)	Control Subjects (n = 36)	p Values
LVDd/BSA (cm/m^2)	3.11 ± 0.28	2.77 ± 0.27	0.001
LVDs/BSA (cm/m^2)	1.85 ± 0.19	1.74 ± 0.22	0.05
Ejection fraction (%)	79 ± 4	75 ± 6	0.01
SVI (ml/beat/m^2)	24.2 ± 6.9	16.4 ± 4.9	0.001
LVSED/BSA (cm/m^2)	0.60 ± 0.06	0.59 ± 0.07	NS
LVPWED/BSA (cm/m^2)	0.60 ± 0.07	0.58 ± 0.07	NS
AoED/BSA (cm/m^2)	1.89 ± 0.17	1.88 ± 0.21	NS
LAED/BSA (cm/m^2)	1.99 ± 0.17	1.91 ± 0.30	NS
Resting heart rate (beats/min)	59 ± 8	67 ± 9	0.001

Values show mean ± standard deviation.
AoED = aortic root at end-diastole; BSA = body surface area; LAED = left atrium at end-diastole; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LVPWED = left ventricular posterior wall at end-diastole; LVSED = interventricular septum at end-diastole; NS = not significant; SVI = stroke volume index.

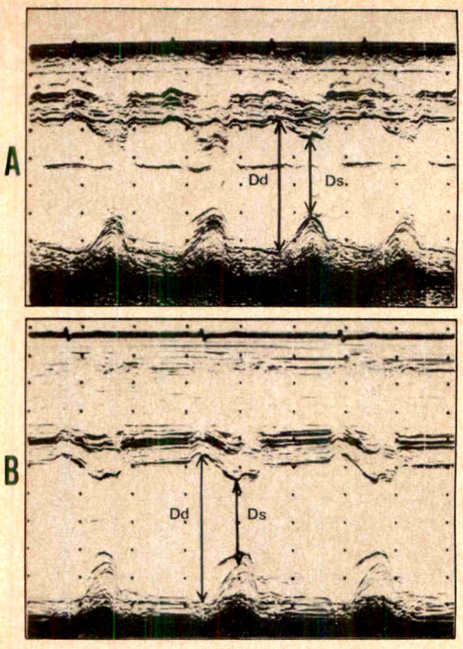

FIGURE 1. Echocardiogram of a healthy man (**A**) and of a patient with vibration disease (**B**). The ejection fraction in **A** was 77% with a left ventricular end-diastolic dimension (Dd) of 46 mm and a left end-systolic dimension (Ds) of 28 mm. The ejection fraction in **B** was 83% with a Dd of 52 mm and a Ds of 29 mm.

of the autonomic function was determined by digital plethysmography with auditory stimuli. The methods and procedures have been described in other reports.[5,6]

To avoid interobserver error, all measurements were made by the same observer and the values were obtained by the mean of 3 consecutive beats. The significance of differences between the means was determined using Student's t test.

Results

Left ventricular ejection fraction and stroke volume: Left ventricular ejection fraction (EF) was significantly higher in patients with vibration disease than in the control subjects. The EF in patients with vibration disease was 79 ± 4% (mean ± SD), ranging from 70 to 86%. In contrast, the EF of the control subjects was 75 ± 6%, a statistically significant difference ($p < 0.01$) (Table I). Left ventricular end-diastolic dimension indexes (LVDd/body surface area [BSA]) of patients with vibration disease and control subjects were 3.11 ± 0.28 cm/m^2 and 2.77 ± 0.27 cm/m^2, respectively. This difference also was statistically significant ($p < 0.001$). Left ventricular end-systolic dimension indexes (LVDs/BSA) of patients with vibration disease and the control subjects were 1.85 ± 0.19 cm/m^2 and 1.74 ± 0.22 cm/m^2, respectively. This difference was statistically significant ($p < 0.05$). The stroke volume index was also significantly higher in patients with vibration disease ($p < 0.001$). Several other echocardiographic measurements, ventricular septum at end-diastole, left ventricular wall at end-diastole, left atrium at end-diastole, and aortic root at end-diastole, were greater in patients with vibration disease than in the control subjects.

Figure 1 illustrates typical echocardiograms from a control man and from a patient with vibration disease. In the control group the EF was 77% with an LVDd of 46 mm and an LVDs of 28 mm. In the group with vibration disease the EF was 82% with an LVDd of 52 mm and an LVDs of 29 mm.

Correlation between left ventricular EF and autonomic nerve activity: Figure 2 illustrates the relation between left ventricular EF and autonomic nerve activity in patients with vibration disease. Autonomic nerve activity from digital plethysmography combined with auditory stimuli was classified into 3 types: normoreactive, hyperreactive, and hyporeactive.[5,6] The EF in the normoreactive, hyperreactive, and hyporeactive autonomic groups was 77 ± 6% (mean ± SD), 80 ± 3%, and 76 ± 2%, respectively. Thus, the EF tended to increase with increasing autonomic nerve activity. In contrast, all control subjects showed normoreactive activity.

Electrocardiographic findings: Table II illustrates the variables of the electrocardiogram. The amplitude of the T waves was analyzed as a ratio to the R waves. From analyses of limb lead I and precordial leads V_5 and V_6, only precordial lead V_6 was significantly greater in patients with vibration disease ($p < 0.05$). Flat T waves in limb leads or in precordial leads were observed in 1 patient with vibration disease and in 3 members of the control group. Using voltage criteria, left ventricular hypertrophy was noted in 5 patients with vibration disease. However, the control group was not indicative of left ventricular hypertrophy. From analyses of ventricular deflections, the sum of $R_I + S_{III}$ in patients with vibration disease was smaller than that in the control group, and the sum of $S_{V_1} + R_{V_5}$ was greater in patients with vibration disease than in the control group.

Resting heart rate in the group with vibration disease was significantly lower than that in the control group ($p < 0.001$). The former was 59 ± 8.1 beats/min, and the latter 67 ± 9.3 beats/min.

Values for blood pressure and the cardiothoracic ratio

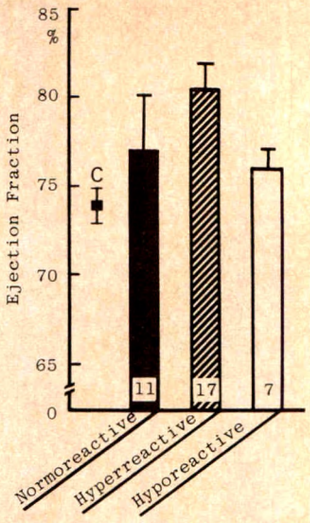

FIGURE 2. Correlation of left ventricular ejection fraction and autonomic nerve activity in patients with vibration disease. The autonomic tones were classified as normoreactive, hyperreactive, and hyporeactive with digital plethysmography combined with auditory stimuli. The ejection fraction (mean ± standard deviation) in the normoreactive (11 patients), hyperreactive (17 patients), and hyporeactive patients (7 patients) was 77 ± 6%, 80 ± 3%, and 76 ± 2%, respectively. Note that the ejection fraction increases with the activity of the autonomic nervous system. C indicates the ejection fraction (mean ± standard deviation) in the control subjects. All of them showed the normoreactive autonomic tones.

were within the normal range in both groups, and no significant differences were observed between the 2 groups.

Discussion

Defense mechanism in vibration disease: During the use of vibrating tools, the human body is exposed to 3 major stressors: vibration, noise, and cold. Typical levels of vibration are from 0.316 to 100 m/s^2 and of noise from 80 to 120 dB(air). These intensities can apparently stress the human body. The stressors may excite the hypothalamus and the limbic lobe in the cortex, in which the higher center of the autonomic nervous system exists. Consequently, the sympathetic tone could be significantly augmented. In these situations, defense mechanisms to the stressors may be provided in the human body, so that an adaptive response can be produced. Thus, habitual operation of vibrating tools may result in the development of mechanisms for adaptation to stress in the human body.

Increased left ventricular ejection fraction: A high incidence of bradycardia and cardiomegaly (cardiothoracic ratio >0.5) and a low incidence of hypertension have been observed in a study of 300 patients with vibration disease.[2] Also, endurance athletes possess resting sinus bradycardia, cardiomegaly, comparatively low blood pressure, increased cardiac output and left ventricular EF, and others.[7] In the present study, an increase was found in left ventricular EF and stroke volume. Left ventricular EF is commonly used as an index of left ventricular function. It is calculated by the

TABLE II Electrocardiographic Findings in Patients With Vibration Disease and Control Subjects

	Patients With Vibration Disease (n = 35)	Control Subjects (n = 35)	p Values
T/R wave ratio			
Lead I	0.399 ± 0.218	0.363 ± 0.206	NS
Lead V_5	0.267 ± 0.140	0.237 ± 0.075	NS
Lead V_6	0.315 ± 0.127	0.239 ± 0.112	0.05
Sum of R_I + S_{III} (mm)	6.1 ± 2.3	7.6 ± 4.2	NS
Sum of S_{V_1} + R_{V_5} (mm)	29.1 ± 9.2	28.0 ± 7.2	NS

NS = not significant.

left ventricular end-diastolic and end-systolic diameters. Echocardiographic study showed that endurance athletes had ventricular enlargement without thickening of the wall,[8] whereas other investigators found both an enlarged ventricular cavity and an increased wall thickness in professional cyclists,[9] basketball players,[10] and long-distance runners.[11] The present study showed a significantly enlarged ventricular cavity and an appreciably enlarged wall thickness. The difference in these findings may depend on the habitual level of physical activity, the type of sporting activity, and the athletes' performance level.[7]

Increased left ventricular EF and stroke volume at rest may be due to a latent cardiac reserve which is present in endurance athletes. These facts in endurance athletes are plausibly an adaptation to severe physical exercise; however, the mechanism responsible for this adaptation is unclear. The most frequently cited explanation involves alterations in the autonomic nervous system.[7]

Mechanism of adaptation: Habitual use of vibrating tools, that is, chronic exposure to vibration, noise, and cold, may produce autonomic imbalances that are related to the severity of vibration disease.[12] Approximately 75% of 300 cases of vibration disease showed autonomic imbalances.[2] In the present study, autonomic imbalances were observed in approximately two thirds of the patients. This is similar to the changes observed in endurance athletes.[7] The human body may adapt to the underlying conditions[4,7]; consequently, cardiovas-

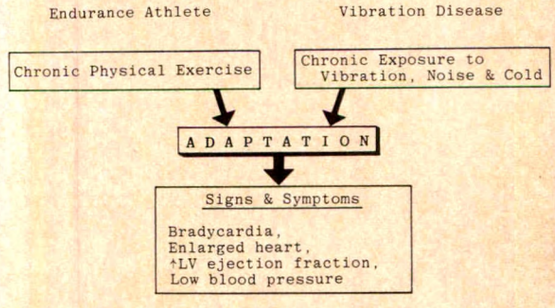

FIGURE 3. A hypothetical scheme illustrating the similarity of the adaptive responses of the cardiovascular system in an endurance athlete and in a patient with vibration disease. LV = left ventricular.

cular signs and symptoms such as bradycardia, enlarged heart, increased left ventricular EF, low blood pressure, and others appear (Fig. 3).

The amplitude of the electrocardiographic T waves, which was expressed as a ratio of the T wave to the R wave, was higher in the group with vibration disease than in the control group. The ratio in precordial lead V_6 was particularly greater than that in the control subjects. Other investigators have described a high amplitude of the T wave in the electrocardiogram of endurance athletes.[13,14] The mechanism of production of the high amplitude T wave is unclear; however the increased amplitude may be a reaction of the heart to stressors. Other findings in the present study generally agree with those of previous studies.[13,14]

Cardiovascular signs and symptoms in patients with vibration disease are relieved approximately 7 years after the use of vibrating tools is stopped.[15] Circumstantial evidence in the present study, such as the high incidence of increased autonomic tone, supports the concept that the cardiac reserve is maintained as an adaptation mechanism for many years.

In conclusion, the cardiovascular signs and symptoms in patients with vibration disease are similar to those frequently observed in endurance athletes. The signs and symptoms may be an adaptive response of the cardiovascular system. Finally, the clinical features in patients with vibration disease include adaptive responses to the stressors as well as direct injuries caused by vibration.

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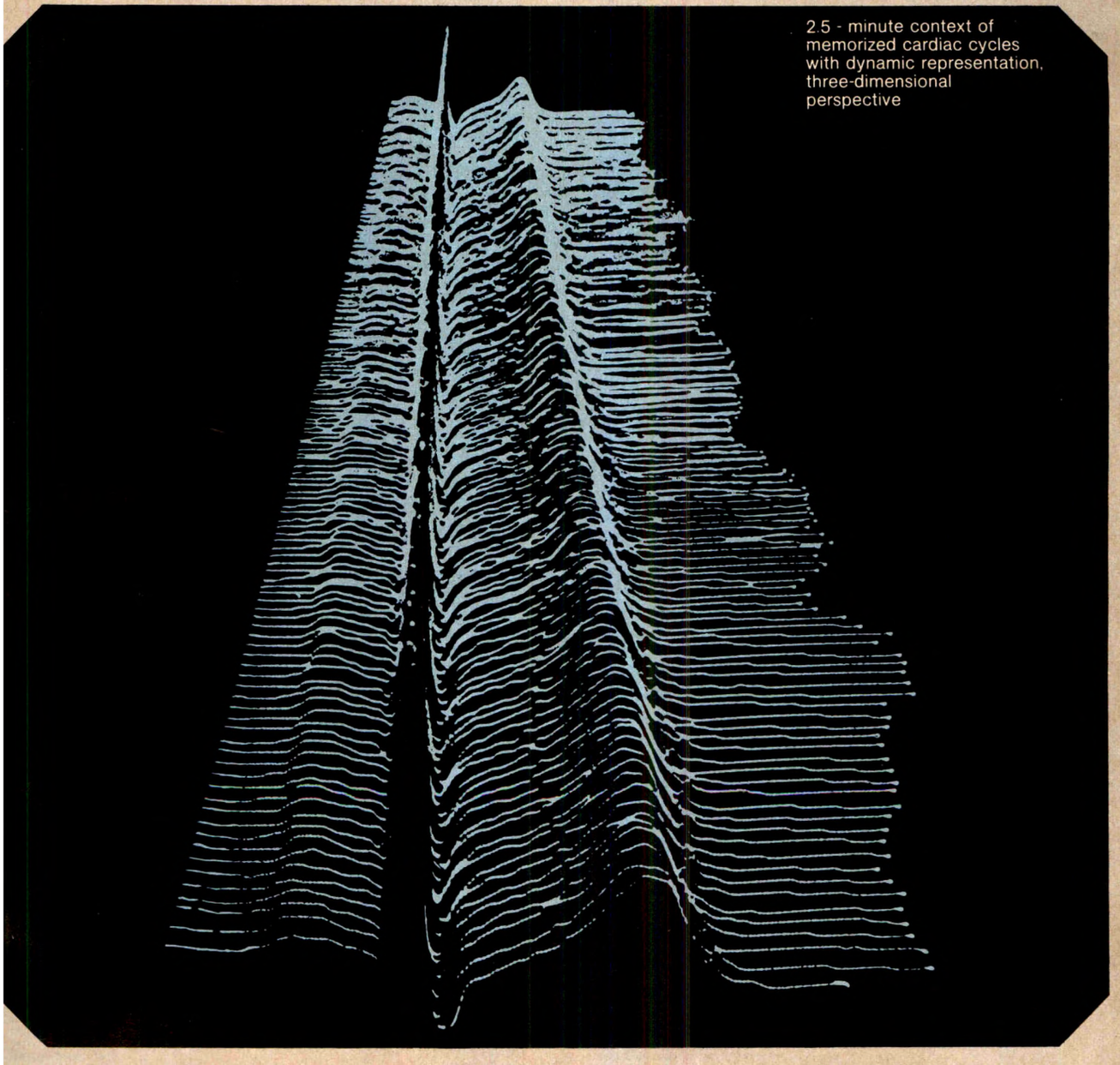

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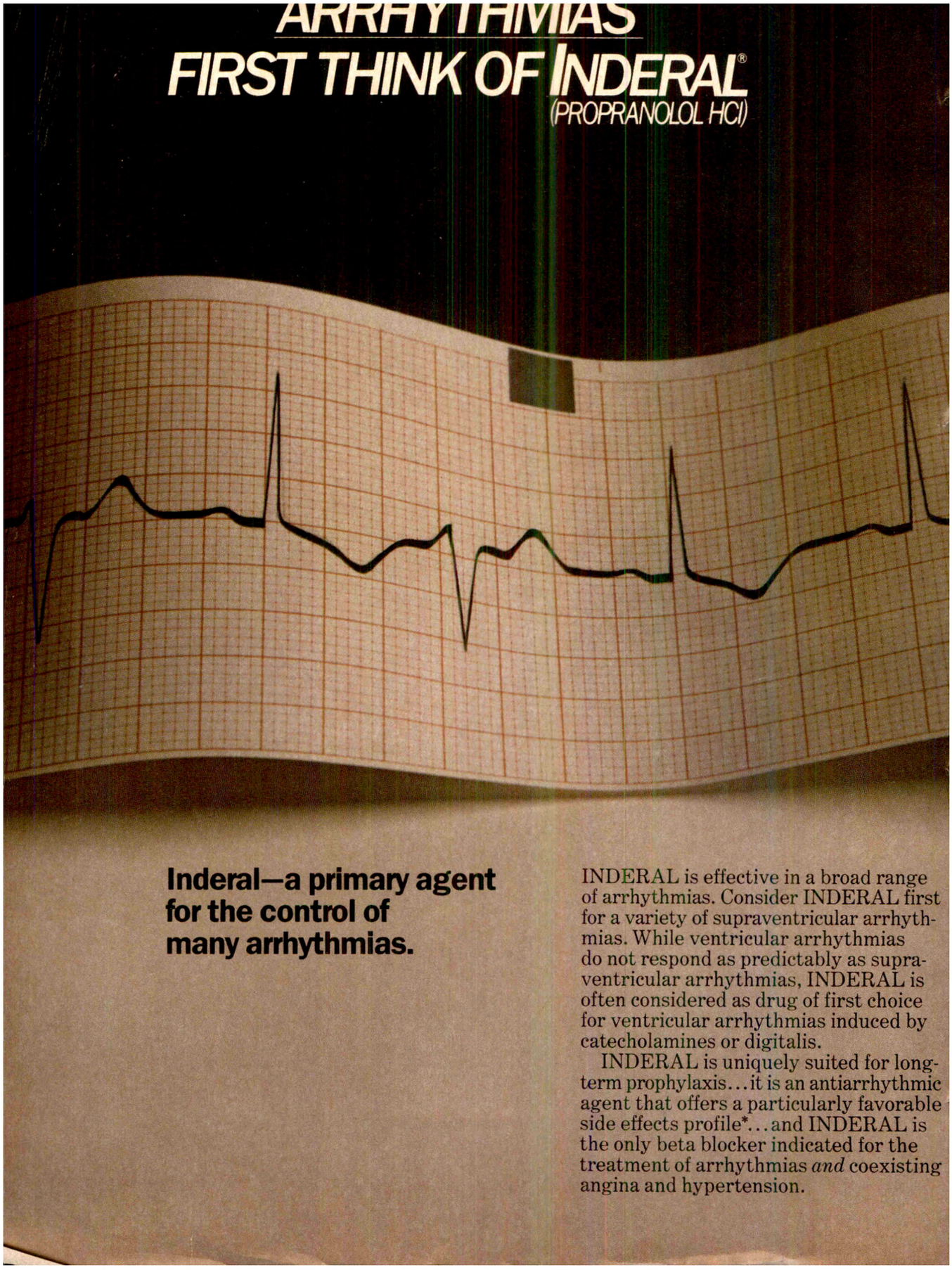

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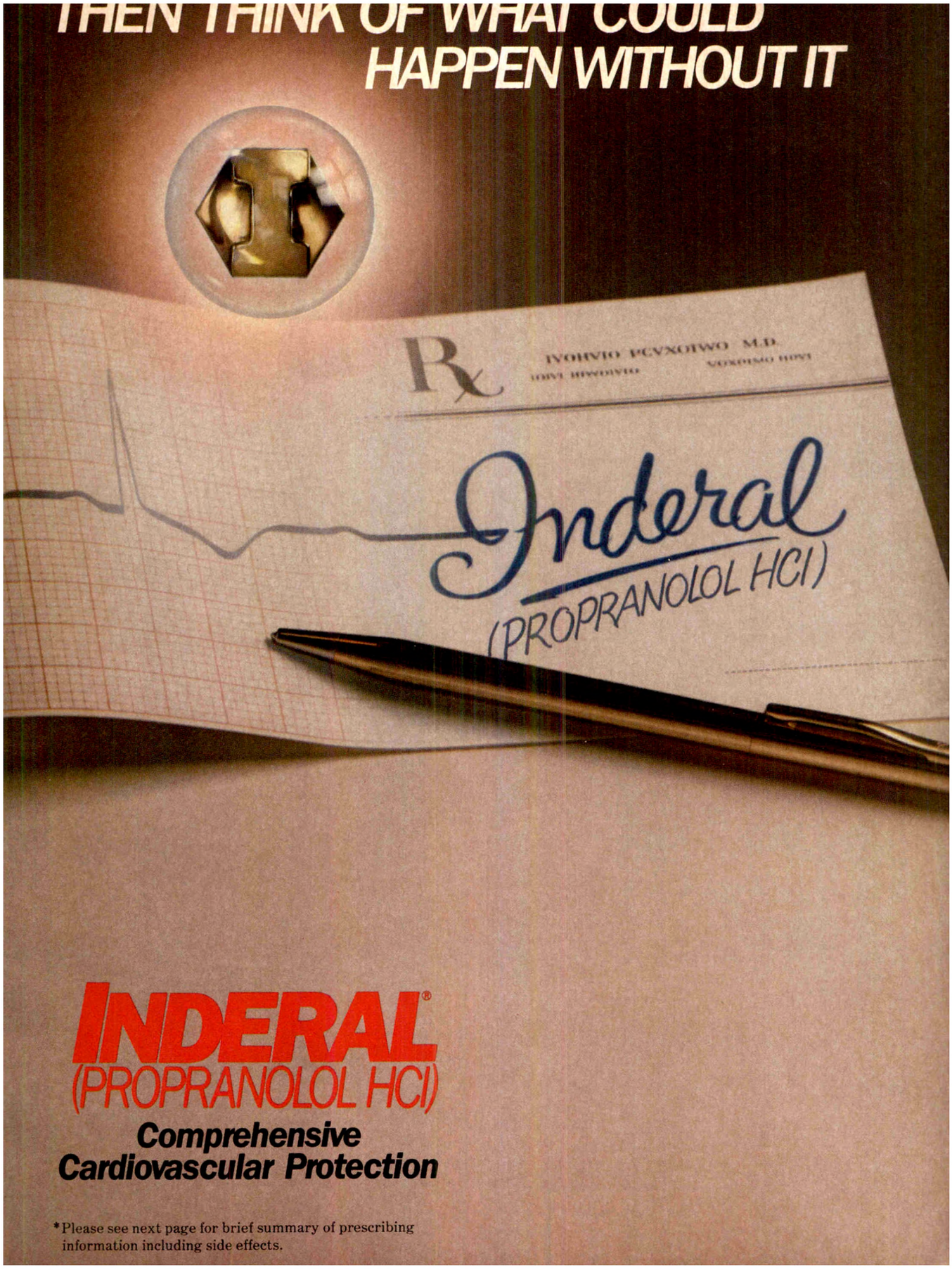

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Propranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may bloc
chodilation produced by endogenous and exogenous catecholamine stimulation
receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta
adrenergic blocking activity, propranolol may prevent the appearance of premonit
and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is
important to keep in mind in patients with labile diabetes. Hypoglycemic attacks m
accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not
established. Use of any drug in pregnancy or women of childbearing potential req
the possible risk to mother and/or fetus be weighed against the expected therape
fit. Embryotoxic effects have been seen in animal studies at doses about 10 times t
mum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be cl
observed if propranolol is administered. The added catecholamine-blocking actio
drug may then produce an excessive reduction of the resting sympathetic nervou
Occasionally, the pharmacologic activity of propranolol may produce hypotension
marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotens

As with any new drug given over prolonged periods, laboratory parameters sho
observed at regular intervals. The drug should be used with caution in patients wit
renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block;
sion; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thron
nic purpura. *Central Nervous System:* lightheadedness; mental depression manife
insomnia, lassitude, weakness, fatigue; reversible mental depression progressing
catatonia; visual disturbances; hallucinations; an acute reversible syndrome chara
by disorientation for time and place, short term memory loss, emotional lability, slig
clouded sensorium, and decreased performance on neuropsychometrics. *Gastro*
nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipatio
teric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosi
erythematous rash, fever combined with aching and sore throat, laryngospasm an
tory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrc
cytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopeci
mucocutaneous reactions involving the skin, serous membranes and conjunctivae
for a beta blocker (practolol) have not been conclusively associated with propran
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with sever
disease, elevated serum transaminase, alkaline phosphatase, lactate dehydroger

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*National survey of 2960 physicians, including 1502 cardiologists and other physicians subspecializing in cardiology, conducted by Hoechst-Roussel Pharmaceuticals Incorporated, Somerville, New Jersey. August, 1982.

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Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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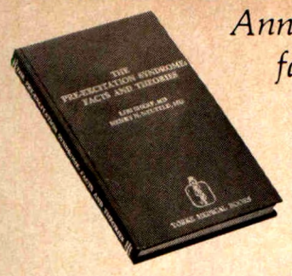

Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

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Henry N. Neufeld, M.D., FACC, Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

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- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

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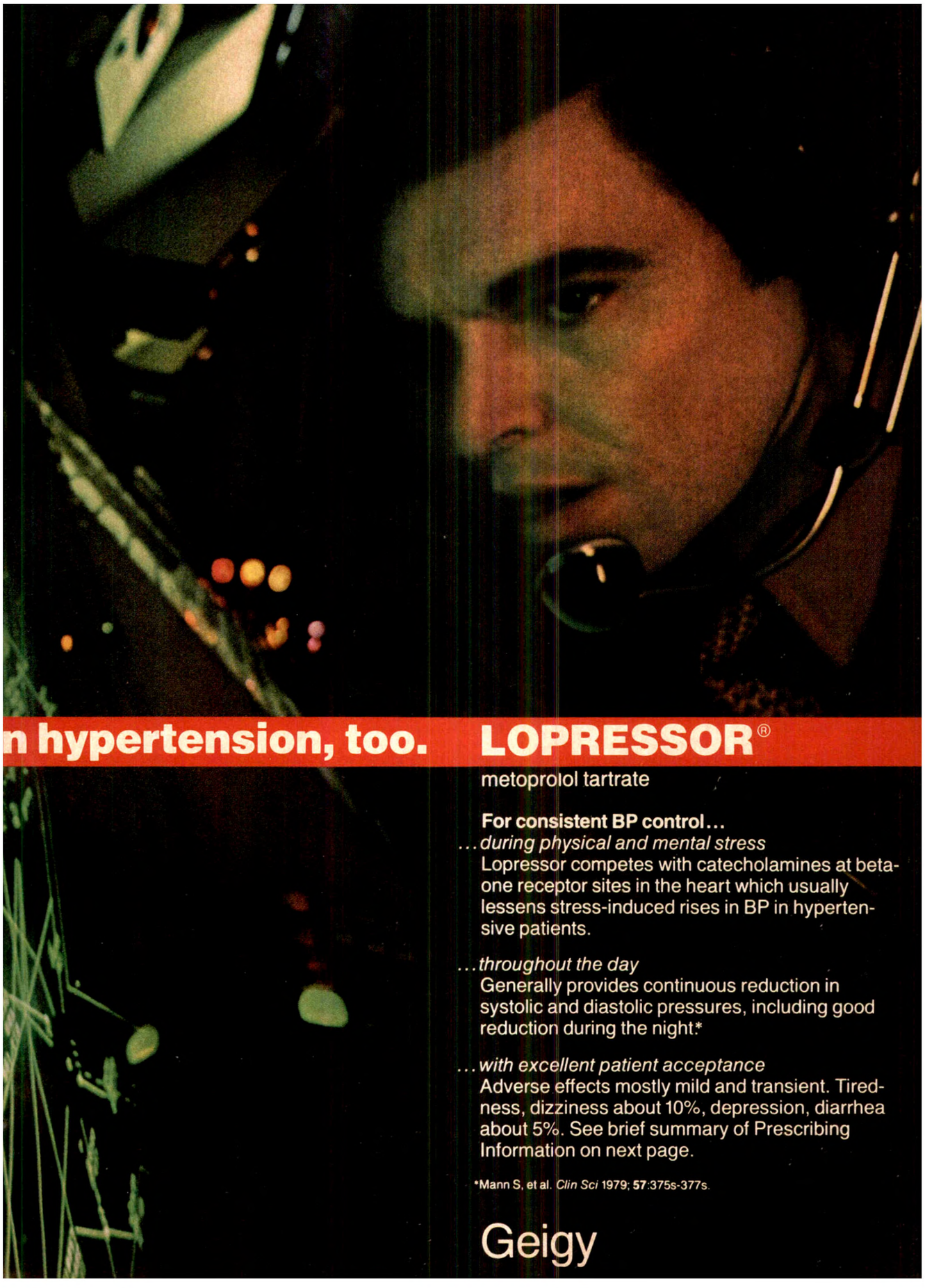

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...*throughout the day*
Generally provides continuous reduction in systolic and diastolic pressures, including good reduction during the night.*

...*with excellent patient acceptance*
Adverse effects mostly mild and transient. Tiredness, dizziness about 10%, depression, diarrhea about 5%. See brief summary of Prescribing Information on next page.

*Mann S, et al. *Clin Sci* 1979; **57**:375s-377s.

Geigy

Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).
Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**
Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.
Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.
Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.
Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.
Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.
Usage in Children: Safety and effectiveness in children have not been established.
Adverse Reactions Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**
Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.
Allergic: Pruritus has occurred in less than 1 of 100 patients.
Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.
Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.
Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics
Cardiovascular: Intensification of AV block (see **Contraindications**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
Miscellaneous: Reversible alopecia.
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.
Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.
This drug should be stored at controlled room temperature and protected from moisture.
How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.
Store at controlled room temperature and protect from moisture.
Dispense in tight, light-resistant container (USP).

C80-82 (12/80)

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Angiographic Demonstration of Coronary Occlusion During Spontaneous Acute Myocardial Infarction and Subsequent Angiographically Normal Coronary Arteries

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The occurrence of acute myocardial infarction (AMI) in a patient subsequently shown to have angiographically normal coronary arteries is at variance with classic concepts regarding the causal relation between AMI and coronary arterial occlusion. Temporary arterial occlusion by spasm[1,2] or thrombus[1,3,4] has been suggested in this circumstance, but no patient has been reported in whom such a sequence was demonstrated.

A 29-year-old previously healthy man was hospitalized for symptoms and electrocardiographic changes of AMI. Selective coronary arteriography peformed 5.5 hours after the onset of symptoms demonstrated occlusion of the proximal left anterior descending (LAD) artery (Fig. 1, top). Left ventriculography demonstrated marked anterior hypokinesia. The right and left circumflex coronary arteries were normal. Intracoronary nitroglycerin (300 μg) did not resolve the occluding lesion, but it was substantially smaller after the administration of 230,000 units intracoronary streptokinase (Fig. 1, center).

Intravenous nitroglycerin and oral nifedipine were begun; later, full-dose anticoagulation was administered. Serum creatine phosphokinase exceeded 2,000 units and included an MB fraction of 19%.

On the 17th hospital day, cardiac catheterization was repeated. Left ventricular end-diastolic pressure was 14 mm Hg. Left ventriculography demonstrated anterior hypokinesia and inferoapical dyskinesia. All major coronary arteries were widely patent (Fig. 1, bottom).

Congestive heart failure progressed thereafter. A cerebral embolism led to death 4 months after the AMI.

At necropsy the heart weighed 480 g, and all 4 cavities were dilated. A transmural scar involved the septal and anterolateral portions of the left ventricular wall, and foci of necrosis were present in the anterior wall. A thrombus overlay the area of fibrosis in the left ventricular apex. The coronary arteries were free of significant narrowing except for a localized 75% cross-sectional area narrowing of the proximal LAD artery by an atherosclerotic plaque (Fig. 2). An embolus was present in the right middle cerebral artery with a resulting cerebral infarct.

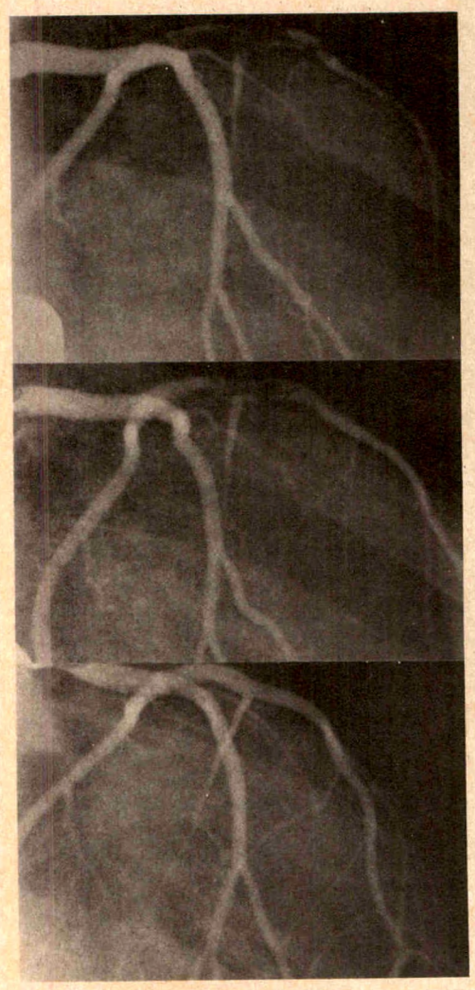

FIGURE 1. Coronary arteriographic views of the left coronary artery in the right anterior oblique projection. The **top panel** was filmed 5.5 hours after onset of AMI. It demonstrates a filling defect producing near-total occlusion of the proximal left anterior descending artery. The **center panel,** filmed after the administration of 230,000 units of streptokinase into the artery, shows striking reduction in the occluding lesion and restoration of distal flow. The **bottom panel,** filmed 17 days later, does not show a detectable lesion.

There are 2 extraordinary features of this case. First, we are aware of no other reports in which a major coronary artery was demonstrated to be nearly totally obstructed "early" after the spontaneous onset of AMI involving the distribution of that artery. On subsequent examination, significant obstruction could not be

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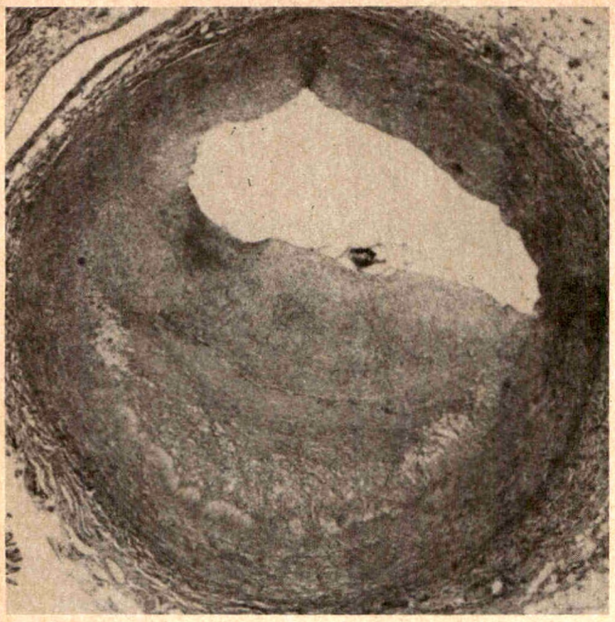

FIGURE 2. Photomicrograph of a cross-section of the proximal left anterior descending coronary artery 4 months after the AMI. (Hematoxylin and eosin stain; magnification ×30, reduced 4%.)

demonstrated either in that coronary artery or in any other. Second, necropsy 4 months after the "normal" arteriogram revealed a significant atherosclerotic lesion at the site of the occlusion demonstrated by angiogram at the time of the AMI (Fig. 2).

At least 2 explanations may be offered for this sequence. One, the coronary arteriograms failed to demonstrate a narrowing which in fact was present. Although it is well known that narrowing may be underestimated by angiography,[5,6] in this case the films were of high quality and in multiple projections, including hemiaxial views. Second, the arteries indeed were free of significant narrowing 4 months before necropsy.

Based on the angiographic appearance of the obstructing lesion in our case, it is reasonable to believe that thrombus plays a major role in the genesis of spontaneous AMI in some patients subsequently shown to have angiographically normal coronary arteries. The reason for clot formation is not clear. It appears reasonable to believe that the atherosclerotic lesion at the site of the previous angiographic obstruction was initiated by organization of the observed thrombus.

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Transient Right Atrial Thrombus During Acute Myocardial Infarction: Diagnosis by Echocardiography

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Echocardiographic diagnosis of right-sided cardiac thrombi is unusual. In the patient described herein, a large right atrial thrombus was detected after inferior myocardial infarction and was likely responsible for both systemic (paradoxical) and pulmonary emboli.

A previously healthy 62-year-old man had an acute inferior wall transmural myocardial infarction, complicated by first-degree heart block. Cardiac catheterization revealed akinesia of the left ventricular inferior wall and slight apical dyskinesia. The right coronary artery was totally occluded, and it failed to open after 250,000 units of intracoronary streptokinase. During catheterization, complete heart block developed and a temporay transvenous pacemaker was inserted into the right ventricle; it was removed 18 hours later.

The hospital course was complicated by pain (thought to represent pericarditis), short runs (5 to 6 beats in duration) of atrial fibrillation, and transient left facial weakness and numbness. A computerized tomographic scan of the head revealed no hemorrhage, and intravenous heparin was, therefore, begun. Echocardiography at that time (Day 10) revealed a large left ventricle with a hypokinetic ventricular septum and apex. No thrombus was visualized within the left side of the heart. A large mass of echoes was apparent within the right atrium attached to the lower lateral right atrial wall by a narrow stalk, which allowed it to prolapse through the tricuspid valve orifice into the right ventricle during diastole. In ventricular systole, in the apical and subxiphoid 4-chamber views, the right atrial mass appeared to push into the atrial septum at the presumed level of the foramen ovale, and in several frames a small part of the mass appeared to enter the left atrium by way of the atrial septum. Lung scan performed later that day demonstrated decreased perfusion, but normal ventilation in the superior segment of the right lower lobe and subsegmental defects elsewhere. By the next day, 2-dimensional echocardiography documented disappearance of the right atrial mass. A repeat lung scan documented the new appearance of decreased perfusion in the left upper and lower lobes compatible with significant recurrent pulmonary emboli. The patient was discharged re-

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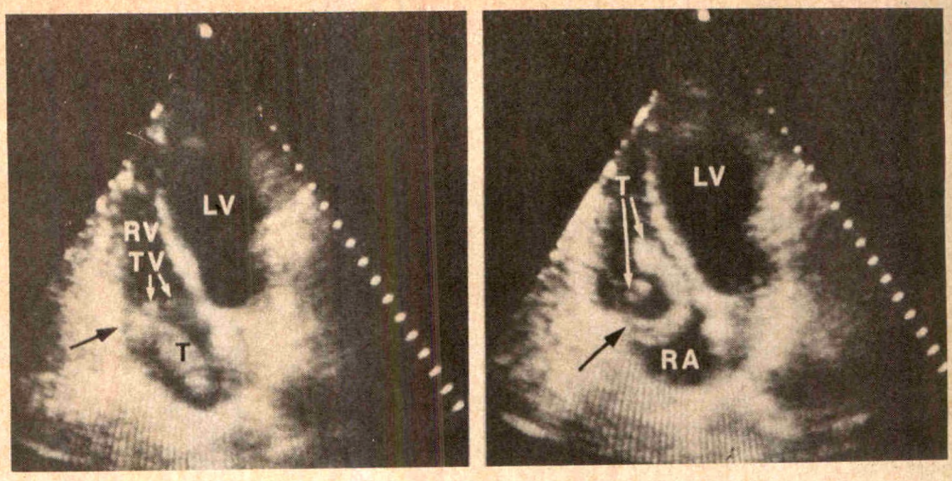

FIGURE 1. Two-dimensional echocardiograms performed with a Hoffrel mechanical sector scanner. Apical 4-chamber views in systole (**left panel**) and diastole (**right panel**) demonstrate the large thrombus (T) attached to the lower lateral wall of the right atrium (RA). LV = left ventricle; RV = right ventricle; TV = tricuspid valve.

ceiving warfarin and digitalis on the 19th hospital day. Out-patient echocardiography 5 months after the myocardial infarction demonstrated no recurrence of the right atrial mass.

To my knowledge, right atrial thrombi have not previously been documented by ultrasound in a patient with acute myocardial infarction. In my patient, it is likely that endothelial damage resulting from the right-sided cardiac catheterization or the subsequent placement and transient presence of a transvenous electrode for temporary pacing provided a nidus for thrombus formation. The short runs of atrial fibrillation in this patient, lasting only 5 to 6 beats at maximum, were likely of too short a duration to produce sufficient stasis for clot formation. The presence of such an unusual complication of both acute myocardial infarction and right-sided cardiac catheterization raises the possibility that streptokinase administration may in some way have permitted thrombus formation. Experience with this patient raises the question of whether patients should be anticoagulated after streptokinase administration, irrespective of achievement of clot lysis.

Extravascular Obstruction of the Superior Vena Cava by Hematoma After Open-Heart Surgery and Diagnosis by Scintigraphy

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Although the superior vena cana (SVC) syndrome has been well studied,[1] its acute occurrence complicating adult open-heart surgery has not been reported. In this setting, the possibility of SVC tamponade due to pericardial hemorrhage and ensuing clot formation must be considered. Postoperative monitoring with an indwelling pulmonary artery balloon flotation catheter can cause acute thrombotic obstruction of the SVC.[2,3] Etiologic distinction is important since the management of extravascular compression is surgical and that of thrombotic obstruction is usually medical. In the latter situation, manipulation of the catheter before the application of thrombotic dissolution therapy could contribute to an adverse outcome.[4] We recently observed SVC syndrome early after open-heart surgery in a patient in whom a balloon flotation catheter was in place. Roentgenographic and scintigraphic findings were important in making the etiologic diagnosis, and hence, in choosing the appropriate therapy.

A 56-year-old woman underwent open-heart surgery because of dysfunction of a Harken prosthesis 12 years after mitral valve replacement. At surgery, dense adhesions from the previous operation were encountered. Replacement of the Harken prosthesis with a St. Jude valve, however, was uneventful. Postoperatively, the patient had a low cardiac index with poor urinary output; 24 hours after surgery, she had marked jugular venous distention without pulsations. Her face, arms, and upper torso had a peculiar bluish discoloration. Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were slightly elevated, and did not respond to volume challenge. Chest roentgenograms (Fig. 1) then showed that the right cardiac silhouette was particularly prominent. Technetium-99m equilibrium blood pool scintigraphy (Fig. 2) yielded an image, obtained 15 minutes after injection, of nearly absent radioactivity bordering the right heart base, including the region where the right atrium would normally be seen. An unusual and irregular concen-

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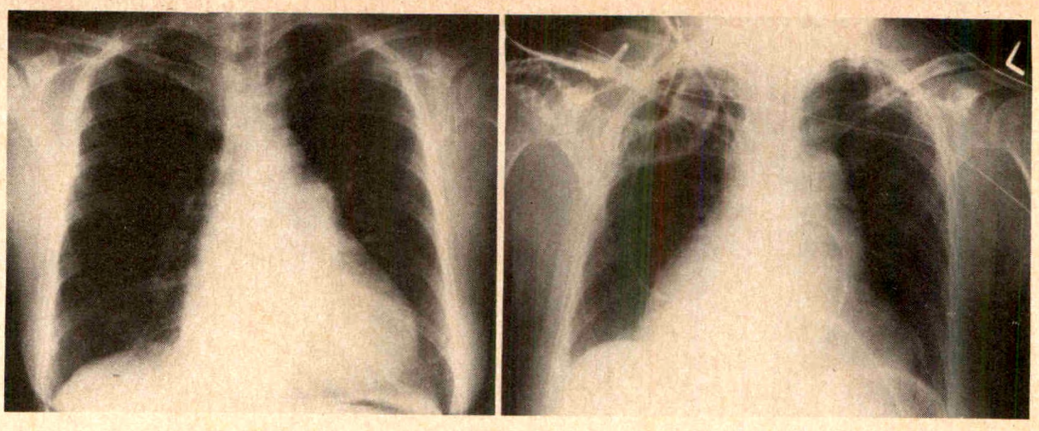

FIGURE 1. Chest x-rays performed immediately preoperatively (**left**) and 24 hours postoperatively (**right**). Marked prominence of the right heart border had developed.

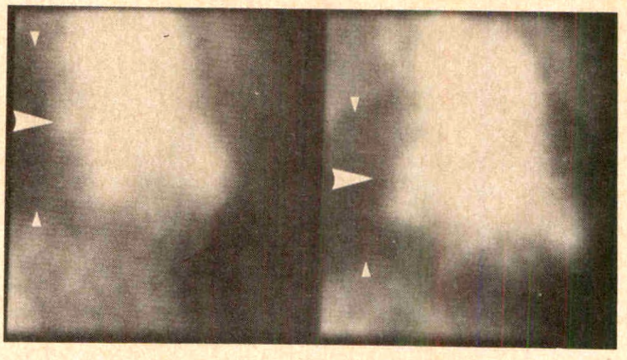

FIGURE 2. Scintigraphic images, anterior position, end-diastolic frames. Fifteen minutes after injection (**left**), there was a small, irregular accumulation of radioactivity (**horizontal arrow**) in a region above the expected position of the right atrium. In addition, there was a large area of absent radioactivity along the right side of the heart (outlined by **vertical arrows** in both images) and in the expected position of the right atrium, probably representing blood and blood clots present from before injection of the labeled red blood cells. One hour after injection (**right**), there was a much larger, more irregular, and immobile accumulation of radioactivity in this area (**horizontal arrow**), indicating the presence of active bleeding.

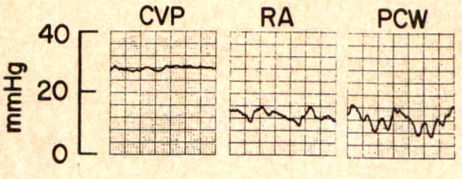

FIGURE 3. Sequential pressure tracings from the tip of pulmonary artery balloon flotation catheter, as it is advanced through the superior vena cava and the right atrium (RA), and into the pulmonary capillary wedge (PCW) position. CVP = central venous pressure.

tration of radioactivity was arising from a site cephalad to the expected position of the right atrium. Repeat imaging 1 hour after injection revealed a marked and immobile expansion of this irregular accumulation of radioactivity in the region of the base of the right side of the heart (Fig. 2). The balloon flotation catheter was withdrawn to the level of the internal jugular vein sheath, and reinserted with continuous monitoring of pressures. The tracings disclosed a markedly elevated, dampened-appearing SVC pressure, with relatively normal right atrial and pulmonary capillary wedge pressures (Fig. 3). The patient was returned to the operating theater, where about 500 ml of freshly clotted blood was found lying alongside and compressing the upper aspect of the right atrium, extending up to and including the SVC at its junction with the right atrium. When this blood was evacuated, the pressure in the SVC dropped markedly. A small arterial bleeding point was noted in the lysed adhesions surrounding the right atrium.

Cardiac tamponade is a common complication of adult open-heart surgery. Occasionally, the tamponade is localized to a single cardiac chamber. Right atrial tamponade may be suspected from comparative right atrial, right ventricular, and pulmonary capillary wedge pressures.[5] Hemorrhagic compression of the SVC may be regarded as a variant of right atrial tamponade, in that the cause is identical but the compression occurs at a higher level. Diagnosis will depend on physical examination if the right atrial pressure port of the pulmonary artery balloon flotation catheter is below the level of obstruction. Chest roentgenography and technetium-99m red blood cell scintigraphy may establish the hemorrhagic cause.[5,6]

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Amiodarone Therapy During Pregnancy

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Amiodarone is a benzofuran derivative which contains 39% iodine by weight. Recently, the presence of a metabolite, desethyl amiodarone, has been noted in the plasma of patients receiving the drug on a long-term basis.[1] The drug is an effective agent for the treatment of refractory ventricular and supraventricular arrhythmias.[2] Its use during pregnancy has been limited by insufficient knowledge of maternal-fetal transfer and the documented adverse effects of excessive iodine.[3,4] Herein, we assess the maternal-fetal transfer of amiodarone and its desethyl metabolite in a patient who required this agent for prevention of life-threatening arrhythmia during pregnancy.

A 27-year-old woman was well and asymptomatic until her first pregnancy; during the last stage of delivery she had atrial fibrillation with a mean ventricular rate of 310 beats/min. This was successfully treated with direct-current cardioversion. The subsequent electrocardiogram and electrophysiologic studies showed the Wolff-Parkinson-White syndrome, type A (Fig. 1). Reentry atrioventricular tachycardia was initiated but promptly degenerated into atrial fibrillation which was conducted by way of the accessory pathway with a mean and shortest R-R interval of 220 and 170 ms, respectively. After intravenous ajmaline (50 mg followed by 30 mg), the ventricular rate slowed but atrial fibrillation persisted. Twenty minutes later, the patient converted spontaneously to sinus rhythm.

The patient refused prophylactic treatment because tachycardia had occurred only once and in association with the stress of childbirth. She was asymptomatic for 2 years, until the 16th week of her second pregnancy, when she had tachycardia that persisted for 2 hours. The patient was brought semiconscious to a local hospital where atrial flutter with a rapid ventricular response was documented; it terminated spontaneously. Treatment was started with quinidine sulfate, 300 mg 3 times daily. The patient was well until 34 weeks when she had another episode of sustained atrial flutter-atrial fibrillation (Fig. 1), which was terminated by direct-current cardioversion (10 J). Quinidine was then stopped and amiodarone started with a loading dose of 800 mg daily for 1 week and a maintenance dose of 400 mg daily thereafter. There were no further episodes and, after induction at 41 weeks, a healthy child was delivered without complication. The infant weighed 3,220 g and had an Apgar score of 9 at 1 minute. During the first 48 hours after birth and during labor, the infant's heart rate was 104 to 120

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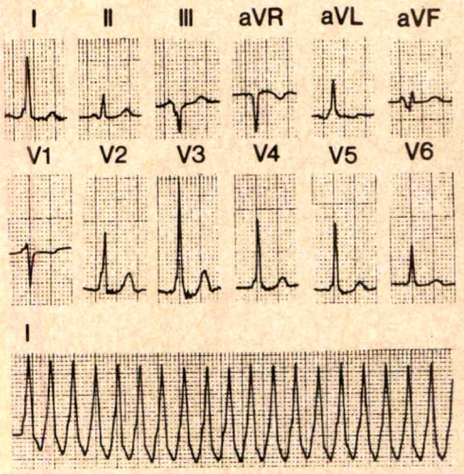

FIGURE 1. Top and center panels, the patient's 12-lead electrocardiogram, demonstrating the Wolff-Parkinson-White syndrome (type A). **Bottom panel,** an episode of atrial flutter with a ventricular rate of 300 beats/min and maximal preexcitation.

TABLE I Maternal and Infant Levels of Amiodarone and Desethyl Amiodarone

Sample	Time	Amiodarone (mg/liter)	Desethyl Amiodarone (mg/liter)
	Mother		
Plasma	8 days prepartum	1.7	1.3
Plasma	At delivery	1.5	1.4
Cord blood	At delivery	0.2	0.4
Breast milk	9 days postpartum	3.6	1.3
Breast milk	11 days postpartum	14.4	5.3
Breast milk	13 days postpartum	13.3	5.7
	Infant		
Plasma	At birth	0.4	0.35
Plasma	2 days	0.4	0.3
Plasma	14 days	0.4	0.25

TABLE II Range of Amiodarone (A) and Desethyl Amiodarone (DA) Concentrations in Breast Milk, Plasma Levels in the Infant and Mother, and the Infant's Estimated Ingestion of A and DA

Weeks Postpartum	Sample	A (mg/liter)	DA (mg/liter)	Estimated Ingestion (mg/kg/day) (Infant)	
				A	DA
6	Breast milk	2.8–16.4	1.1–6.5	1.5	0.7
	Plasma (infant)	0.4	0.25		
9	Breast milk	3.7–14.6	1.2–5.7	1.4	0.5
	Plasma (mother)	1.6	1.5		
	Plasma (infant)	0.4	0.15		

beats/min (normal 120 to 160) and the systolic blood pressure was 66 mm Hg (normal for age). Perfusion was normal, he behaved normally, and there was no goiter or corneal abnormality. Thyroid and liver function test results were normal.

The concentration of amiodarone and its desethyl metabolite in plasma and other biologic fluids was measured using a specific high performance liquid chromatographic technique.[1] *The results from samples collected from the mother and infant up to 2 weeks after the birth are shown in Table I. The infant was breast-fed, and over the subsequent 9 weeks samples of milk were expressed and submitted for the measurement of amiodarone and its desethyl metabolite. Up to 7 samples were expressed over a 24-hour period; the results for 2 such days are shown in Table II. Using a standard table relating age and breast milk intake, the infant's estimated ingestion of amiodarone and desethyl amiodarone are also shown (Table II).*[5]

Atrial fibrillation complicating the Wolff-Parkinson-White syndrome is a potentially lethal arrhythmia. When it occurs during pregnancy, there is a risk to the fetus from the associated hemodynamic changes and from the antiarrhythmic treatment. The aims in prophylaxis are (1) to prevent atrial and ventricular extrasystoles which may initiate reentry tachycardia or atrial fibrillation, and (2) to impair accessory pathway conduction and thereby slow the ventricular response were atrial fibrillation to occur. Conventional agents (quinidine, disopyramide) may be successful in preventing atrial fibrillation, but they are usually less effective in suppressing very rapid (mean ventricular rate 300 beats/min) accessory pathway conduction; this was the case in our patient.

Our recent experience has shown that amiodarone will prevent paroxysmal atrial fibrillation and will adequately attenuate even very rapid accessory pathway conduction.[7] We were, however, loathe to use this agent early in pregnancy because of the theoretical risk to the fetus. Amiodarone, 200 mg, contains approximately 75 mg of iodine within its structure. The precise fate of this large amount of iodine is uncertain.[8] Iodine is known to be (1) transferred rapidly across the placenta even against a concentration gradient,[4] (2) concentrated in fetal thyroid from as early as 14 weeks, and (3) associated with neonatal goiter after as little as 12 mg of iodine is ingested.[9] The risk of such complications for the individual patient is unpredictable and a genetic predisposition to develop goiter has been suggested.[10] In addition, the use of amiodarone during pregnancy carries the possible risk of teratogenic effects on the fetus from the compound. Nevertheless, in our patient the necessity of controlling these life-threatening episodes outweighed the risks of using amiodarone.

The maternal plasma levels of amiodarone and the desethyl metabolite remained stable after the loading period and were consistent with a dose of 400 mg daily.[11] At birth, the neonatal levels were approximately 25% of the maternal levels, indicating limited placental transfer of at least the parent compound and probably the metabolite. This infant who was exposed to amiodarone only during the last month of fetal life and was healthy with normal thyroid and liver function at birth was, however, bradycardic, and this may have been a reflection of the electrophysiologic effects of the drug. Demonstration of maternal fetal transfer of amiodarone indicates that administration of this drug earlier in pregnancy would have resulted in more prolonged exposure.

There was a wide variation in the concentrations of amiodarone and desethyl amiodarone in breast milk throughout the day, emphasizing the need to collect multiple samples for an accurate measurement of drug ingestion, as noted for other drugs.[12] Concentrations of the parent compound in breast milk were higher than the metabolite, probably reflecting the greater lipid solubility of the former. The estimated ingestion of amiodarone by this breast-fed infant was equivalent to a low maintenance dose (for example, 100 mg daily for a 70 kg adult). This was reflected in the infant's plasma levels, which did not vary significantly during the period of our measurements. In addition, desethyl amiodarone, the pharmacologic action of which is not yet known, was also excreted in breast milk. Our data suggest that breast feeding while receiving amiodarone could expose the developing infant to significant doses of the drug and should be avoided.

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High-Degree Atrioventricular Block After Radiation Therapy

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With increasing application of megavoltage radiation therapy, radiation-induced heart disease has become a significant cause of morbidity in patients surviving neoplastic disease. The clinical manifestations of radiation heart disease may not be apparent for years after therapy and include pericardial effusion, acute pericarditis, constrictive pericarditis, "cardiomyopathy," coronary artery disease, and valvular regurgitation, in decreasing order of frequency. Disorders of the specialized conduction system have received little attention. We present a case of high degree atrioventricular (AV) block after radiation therapy.

A 26-year-old man presented in 1966 with bilateral axillary adenopathy and biopsy of an involved node was consistent with Hodgkin's disease (lymphocyte-predominant type). The patient received 4,000 rads of cobalt therapy in a mantle distribution over 22 treatment fractions, with the cardiac apex shielded. No chemotherapy was given. In January 1982, the patient began having syncopal episodes. An electrocardiogram demonstrated right bundle branch block (BBB) with first-degree atrioventricular (AV) block (Fig. 1a); 24-hour ambulatory electrocardiographic recordings were normal. On electrophysiologic study, the AV nodal conduction time was normal, the infranodal conduction time (H-V interval) was 65 ms (normal <55 ms), and there was an infranodal block during incremental right atrial pacing. No supraventricular or ventricular arrhythmias could be induced with programmed stimulation. Syncope occurred spontaneously in the hospital, and an electrocardiogram revealed high-degree AV block (Fig. 1b). There was no change in degree of AV block or in ventricular rate after the intravenous administration of 1.0 mg of atropine. Intravenous epinephrine increased the ventricular rate with return of consciousness. A permanent pacemaker was inserted.

Over the next 6 months, exertional dyspnea developed. Examination was consistent with constrictive pericarditis, which was confirmed by cardiac catheterization. Coronary angiography was normal. Pericardiectomy was followed by relief of dyspnea.

Complete AV block from tumor invasion of the conduction system has occurred with Hodgkin's lymphoma and other tumors; however, direct inspection of the heart and pericardium in the present case revealed no evidence of this. We believe that AV block and constrictive pericarditis in this patient were sequelae of previous mediastinal irradiation.

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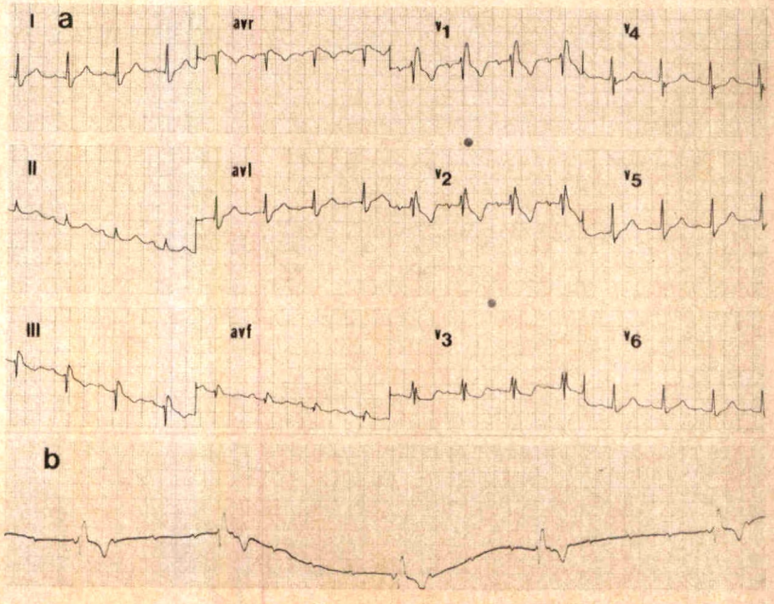

FIGURE 1. a, admission electrocardiogram demonstrating right bundle branch block and first-degree AV block. **b,** rhythm strip demonstrating high-degree AV block occurring during spontaneous episode of syncope (lead V_1).

TABLE I Summary of Previous Reports of Radiation-Induced High-Degree AV Block

Report	Age (yr) at Treatment	Radiation Dose and Field	Chemo-therapy	Years to Onset of High-Degree AV Block	Associated Findings
Rubin et al[1]	44	"Massive"	0	23	Left BBB
Ali et al[2]	19	5,000 rads to heart	+	6	Right BBB, LAFB, pericarditis
Tzivoni et al[3]	32	6,000 rads parasternal	0	18	Second-degree AV block
	40	3,700 rads left thorax	0	23	Second-degree AV block
Cohen et al[4]	20	4,000 rads mantle	+	11	Pleuropericarditis
Patri and Patri[5]	68	4,600 rads left bronchus	0	1	Second-degree AV block

LAFB = left anterior fascicular block.

Conduction disorders reported after radiotherapy to the chest include right BBB, left BBB, right BBB and left anterior fascicular block, right BBB and left posterior fascicular block, and second- and third-degree AV block. Including the present case, there are 7 reports of high-degree AV block after radiation therapy[1–5] (Table I). All patients received ≥4,000 rads to the chest. The interval to development of high-degree AV block ranged from <1 to 23 years (median 14). Preexistent BBB, second-degree AV block, or pericardial disease was common. All patients had symptoms necessitating implantation of a permanent pacemaker. In 1 previous case, a His bundle electrogram demonstrated the level of AV block to be within the AV node.[4] In other cases, the level of AV block was not documented; however, surface electrocardiographic recordings suggested an equal frequency of AV nodal and infranodal block. In the present case, the lack of response to atropine during AV block suggests that the level of the block was infranodal. That the QRS morphology during high-degree AV block was identical to that present during periods of 1 to 1 AV conduction strongly suggests that the level of AV block was intra-Hisian.

High-degree AV block is a potential late complication of megavoltage radiation therapy to the chest. AV block may occur at or below the level of the AV node and usually requires pacemaker therapy. Associated radiation-induced cardiac abnormalities are common.

Acknowledgment: We appreciate the expert editorial assistance of Mary Ellen Denison.

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Amyloidosis Limited to Small Arteries Causing Angina Pectoris and Sudden Death

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Amyloid deposits occur in 2 locations in body organs: *interstitium* and *blood vessels*. Of 54 patients with cardiac amyloid causing cardiac dysfunction studied in our laboratory, 53 (98%) had amyloid deposits involving both interstitium and blood vessels and 1 (2%) had amyloid deposits limited to blood vessels. Because only 2 other patients with amyloid limited to blood vessels have been reported, to our knowledge,[1,2] a brief summary of our case appears justified.

The patient was a 61-year-old woman who presented at age 56 years with inflamed eyelids, and work-up at that time disclosed the presence of immunoglobulin A (IgA)-myeloma. She received chemotherapy. At age 58 years (about 36 months before death), she developed chest pain diagnosed as angina pectoris and she was treated with isosorbide dinitrate and propranolol. She died suddenly at home.

Necropsy (SH#A81-47) disclosed amyloid deposits in blood vessels in virtually every body organ other than the brain without amyloid deposits in the interstitium of any body organ. The deposits involved the blood vessels in some organs—the heart, lungs, bowel, and skin—to a much greater extent than those in other organs. The deposits severely narrowed the lumens of many vessels but no organ infarcts occurred. The deposits were limited to the small intraorgan blood vessels (Fig. 1).

In the heart, amyloid was present not only in the intramural coronary arteries but also in the mural endocardium of all 4 chambers, particularly the atria, and in all 4 cardiac valves. (These structures may be considered modified

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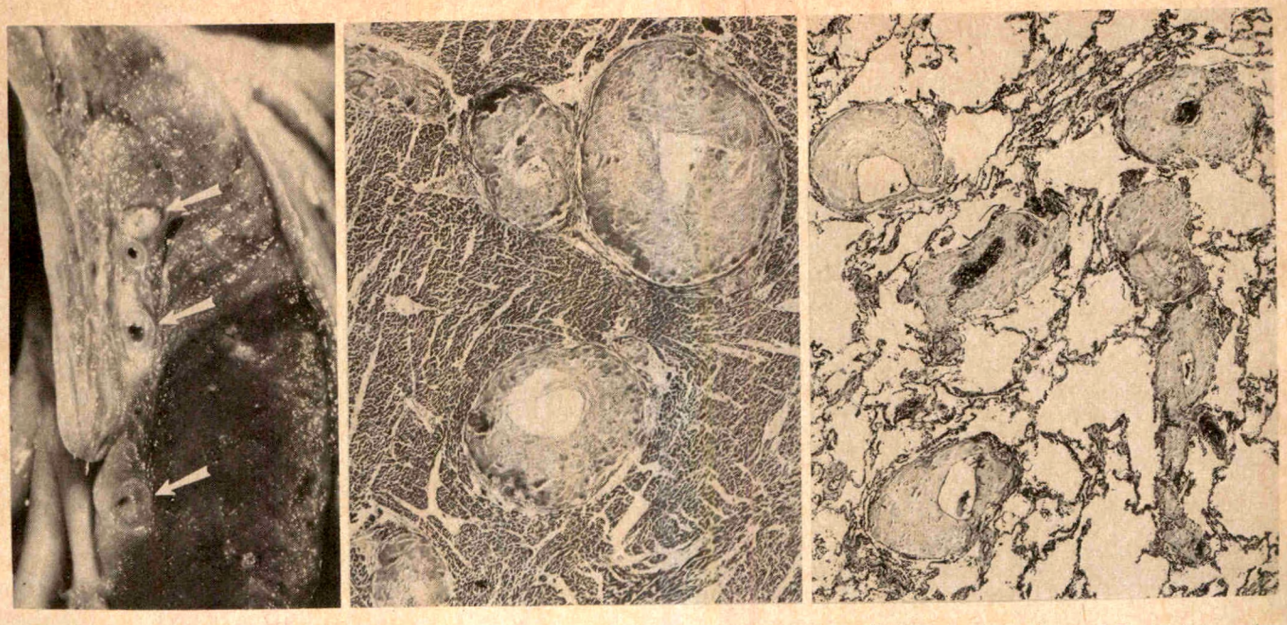

FIGURE 1. Longitudinal cut of ventricular septum (**left**) shows severe thickening of several intramural coronary arteries (**arrows**). Photomicrographs of left ventricular myocardium (**center**) and lung (**right**) reveal amyloid deposits in multiple arteries leading to luminal narrowing. No amyloid deposits are present in the interstitium. (Photographs by M.M.M. Moore.)

blood vessels because they are lined by endothelium.) In contrast, no deposits were located in the myocardial interstitium. The epicardial coronary arteries were free of significant narrowing and amyloid deposits.

Each of the 2 previously reported patients with amyloid confined to the vascular system also had angina pectoris without significant narrowing of the epicardial coronary arteries. Thus, amyloid confined to small (intramural) coronary arteries can cause angina pectoris and fatal cardiac arrest.

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Anomalous Right Coronary Artery: A Surgically Correctable Cause of Angina Pectoris

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Anomalous origin of the left coronary artery has been associated with sudden death in infancy and childhood and with clinically apparent ischemia in adult life.[1]

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Anomalous aortic origin of the right coronary artery (RCA) has usually been regarded as an incidental finding.[2] Indeed, angina pectoris occurring in patients with such anomalous origin of the RCA has almost invariably been described in conjunction with significant coronary atherosclerosis. We here describe a patient with severe angina but free of significant atherosclerosis whose symptoms appeared to be caused by compression of an aberrant RCA between the aorta and right ventricular infundibulum.

A 65-year-old artisan developed angina pectoris at age 58 years (in 1974). Coronary angiography disclosed an aberrant origin of the RCA from the left main coronary artery (Fig. 1, top panels). The anomalous vessel was large and, like the left, free of all but minor atherosclerotic narrowing. The patient was treated with propranolol and nitrates and for 2 years his symptoms were well controlled. Then, over the next 3 years, the angina progressively worsened to the point that he was confined to a wheelchair and became totally dependent upon his wife for even basic needs such as bathing and dressing. Repeat catheterization disclosed normal intracardiac pressures and all 3 major coronary arteries were clearly free of any significant narrowings with the exception

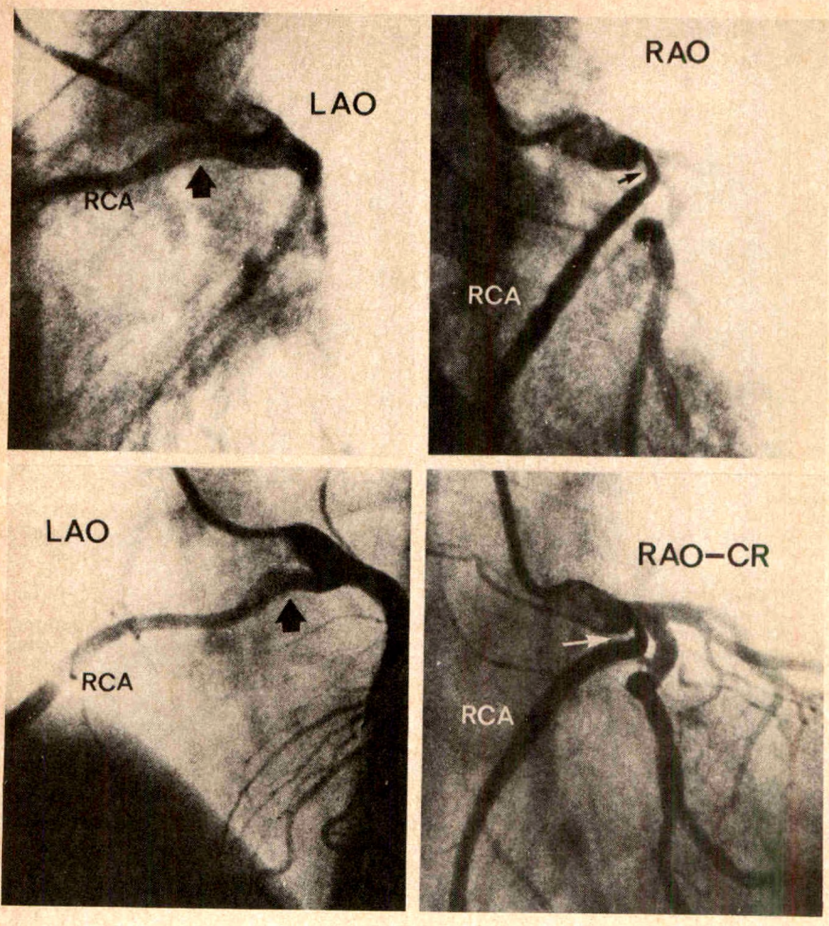

FIGURE 1. Coronary angiogram from the cardiac catheterization studies performed in 1975 (**top panels**) and 1981 (**bottom panels**). In the 1975 study, the **left panel** is a left anterior oblique (LAO) and the **right panel** a right anterior oblique (RAO) view. The right coronary artery (RCA) arises proximally from the left main coronary artery. On close inspection the proximal portion of the RCA appears smoothly narrowed (**arrow**) in the RAO view, but this segment is partly obscured by the vessels it overlies. In the LAO view the proximal segment of the RCA appears widened (**arrow**), but in this projection this segment is superimposed on the catheter. In the 1981 study (**bottom panels**), the **left panel** is also a perpendicular LAO view and the **right panel** a right anterior oblique view with cranial angulation (RAO-CR). In the RAO-CR view, the proximal segment of the RCA is clearly separated from the other vessels and shows a smooth and critical narrowing (**arrow**). In the perpendicular LAO view, this same proximal segment of the RCA is separated from the catheter and appears flattened and wider than the rest of the RCA (**arrow**). These 2 views therefore give the appearance of external compression of the proximal segment of the RCA as it passes between the 2 great vessels.

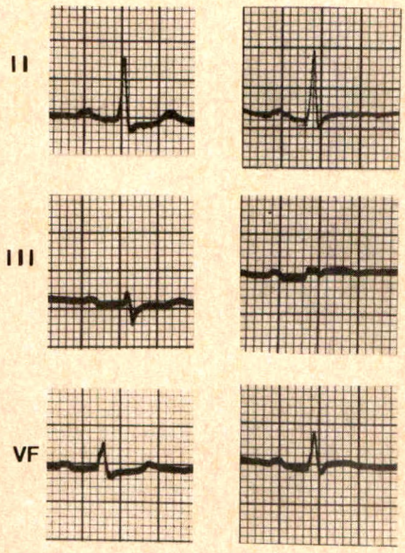

FIGURE 2. Electrocardiographic pacing study. **Left panel,** preoperative study. After pacing at 150 beats/min for 3 minutes, the patient had severe angina and 1 mm of S-T depression was seen in leads II, III, and aVF. **Right panel,** postoperative study. After pacing at 150 beats/min for 9 minutes without symptoms, no inferior S-T or T-wave changes appeared. Both tracings were taken immediately after cessation of pacing.

of a discrete segment of the anomalous RCA, which appeared critically narrowed where it passed between the aorta and right ventricular infundibulum. This segment was narrowed in the cranially angulated right anterior oblique view (a view not performed at the first catheterization) and widened in the perpendicular left anterior oblique view, giving the appearance of a "ribbon-like" external compression between the 2 great arteries (Fig. 1, bottom panels). The left ventriculogram was normal. On exercise, the patient developed severe angina within 30 seconds at a heart rate of 75 beats/min; S-T segment changes in the inferior leads were equivocal. When paced from the right atrium at 150 beats/min for 3 minutes, the patient had severe angina and 1 mm S-T segment depression in leads II, III, and aVF (Fig. 2, left panel). A thallium perfusion scan performed simultaneously showed hypoperfusion of the inferior wall which reperfused 3 hours later.

A single saphenous vein graft was placed to the RCA. Surgery was uneventful and the patient made a rapid recovery. His symptoms were totally relieved and he gradually resumed an active existence. Repeat pacing study 2 months after operation during which the patient was atrially paced at 150 beats/min for 9 minutes failed to produce symptoms or inferior electrocardiographic changes (Fig. 2, right panel) and the thallium perfusion scan was normal. He also completed 9 minutes of a standard Bruce exercise tolerance test without angina and without evidence of ischemia in the inferior leads.

In this case, a congenital anomaly of the RCA appears to be the cause of angina pectoris which first presented in middle age, followed a progressive and disabling course, and was completely relieved by coronary artery bypass surgery. A unique finding is the apparent external compression of the anomalous portion of the artery as it passes between the aorta and right ventricular infundibulum in the absence of any significant obstructive coronary atherosclerotic lesions. In an autopsy series of 10 patients with anomalous origin of the RCA from the left sinus of valsalva, Roberts et al[3] suggest that a possible mechanism of ischemia in these patients is the compression of the anomalous artery between the aorta and pulmonary trunk during exercise. We believe our case to be the first angiographic demonstration of such external compression of an anomalous RCA. This hypothesis is further supported by Liberthson's[2] demonstration of hypoplasia of the anomalous portion of an aberrant RCA at autopsy. The development of symptoms at age 59 in our case may be explained by progressive hypoplasia of the initial segment of the aberrant RCA or enlargement of the pulmonary trunk and aorta with age, or both.

Thus, anomalous RCA may be a rare cause of angina in middle-aged patients and results from compression of the anomalous artery between the great arteries. Multiple views in both oblique positions with hemiaxial angulation may be required at coronary angiography to demonstrate such external compression. Stress myocardial imaging with thallium-201 can be helpful in demonstrating hypoperfusion. Surgical bypass of the anomaly may relieve symptoms.

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Bidirectional Blood Flow in Angiographically Normal Coronary Arteries

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Bidirectional coronary flow is a frequent angiographic finding in patients with severe coronary artery stenosis[1] and after aortocoronary bypass.[2] Under normal physiologic conditions, although small coronary anastomotic channels do exist, they are functionally unimportant[3] and are not demonstrable by angiography.[4] We recently observed bidirectional flow in a patient without obstructive coronary disease.

A 56-year-old man underwent diagnostic cardiac catheterization and coronary angiography for evaluation of recent onset chest pain. Left bundle branch block had been present for years. Left ventricular and aortic pressures were normal and so was left ventricular function by angiography (Fig. 1). Selective coronary artery visualization ruled out obstructive disease and showed clear-cut evidence of bidirectional flow in the posterior descending branch of the right and in the distal circumflex branch of the left coronary artery (Fig. 2 and 3). There was obvious continuity between the distal segments of right and circumflex arteries with the most narrow point measuring about 1 mm in diameter (catheter tip used as a reference).

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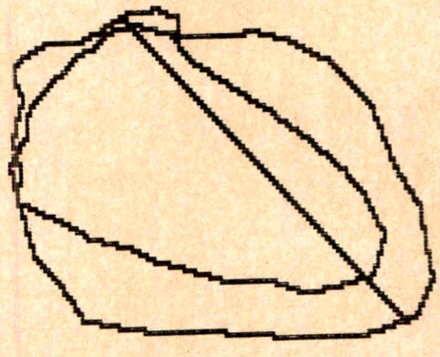

FIGURE 1. Computer-generated plot of the left ventricular end-systolic and end-diastolic contours, axis shifted.

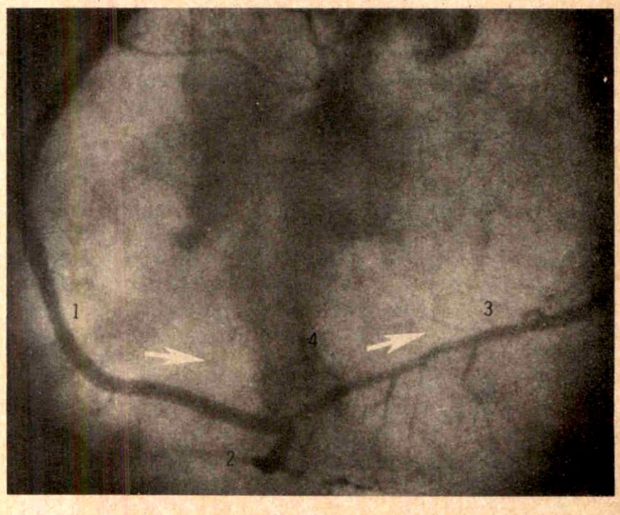

FIGURE 2. Right coronary injection in left anterior oblique projection. **Arrows** indicate the direction of blood flow. 1 = right coronary artery; 2 = posterior descending artery; 3 = distal circumflex artery; 4 = atrioventricular nodal branch.

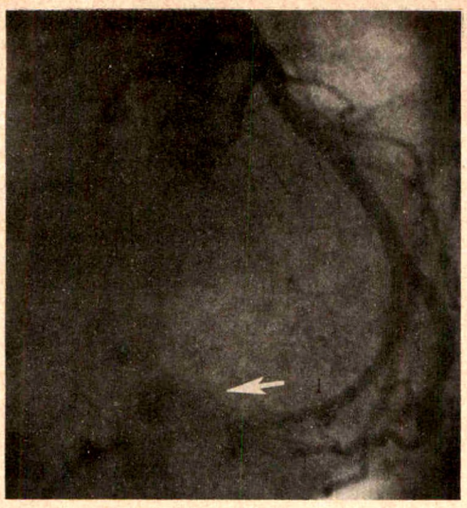

FIGURE 3. Left coronary injection in left anterior oblique projection. 1 = distal circumflex artery; 2 = atrioventricular nodal branch; 3 = posterior descending artery.

While the normal coronary circulation is functionally closed-ended, the pattern of the case presented is open-ended, similar to the circulation of the brain and extremities. We believe that this anomaly is of a congenital nature, since large anastomotic channels have been shown to regress once the situation causing their development is removed.[5] We also believe that bidirectional flow of this nature does not disturb the function of the coronary circulation, but rather would represent a potential "self-cure" for obstructive coronary disease.

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Effect of Steroids on Postoperative Constrictive Pericarditis

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Recently, constrictive pericarditis has become recognized as a complication of cardiac surgery in the absence of sepsis. Six cases had been reported before 1979.[1–4] In 1979, however, 13 additional cases were reported,[5–7] confirming that constrictive pericarditis is a rare but clinically important complication of cardiac surgery. Of the cases reported, all but 4 (2 diagnosed postmortem,[1–3] 2 managed medically[6]) have undergone pericardiectomy. This report documents 3 additional cases of pericardial constriction and suggests a mode of therapy that may eliminate the need for pericardiectomy.

Case Summaries

SH, a 15-year-old black girl, had reimplantation of an anomalous left coronary artery from the pulmonary artery to the aorta in April 1979. After surgery, postpericardiotomy syndrome developed with an effusion noted on echocardiography. Treatment with indomethicin and aspirin resolved the symptoms and signs within 2 weeks. Five weeks postoperatively, she had fatigue and chest pain atypical for angina. Physical examination disclosed jugular venous distention, Kussmaul's sign, and a loud pericardial knock. No pulsus paradoxus, friction rub, or edema were noted. Apexcardiography and phoncardiography (Fig. 1, left) revealed systolic retraction and a loud pericardial knock. Echocardiography showed paradoxical septal motion but no pericardial effusion. Right-sided cardiac catheterization revealed a diastolic plateau of 17 mm Hg and a typical "square-root" sign in the right ventricular pressure tracing. The patient was treated with prednisone, 10 mg twice daily, for 3 weeks. The dose was tapered over the subsequent 3 weeks. Symptoms resolved over 3 weeks, and repeat apexcardiography with phonocardiography in December 1979 showed no systolic retraction or pericardial knock (Fig. 1, right). Three years after surgery, there were no symptoms or signs of constriction.

EH, a 56-year-old black woman, underwent mitral valve replacement in October 1979 without complications. Four weeks after surgery, she had chest pain atypical for angina and dyspnea on exertion. Examination revealed hepato-

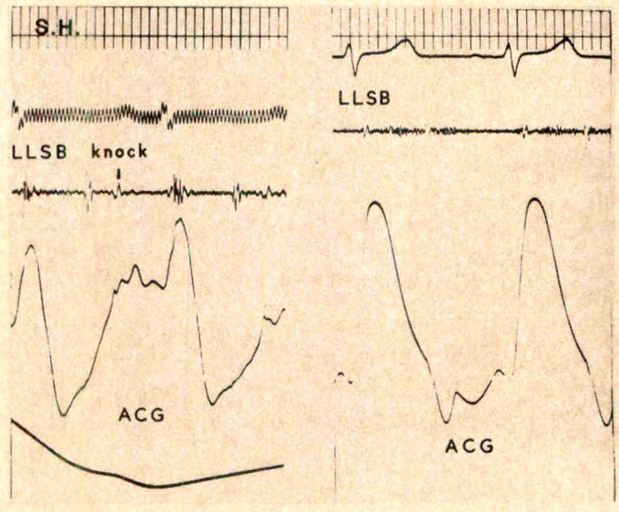

FIGURE 1. Patient SH. **Left,** before steroid therapy, a phonocardiogram showing a loud pericardial knock, and apexcardiogram (ACG) showing systolic retraction. **Right,** after steroid therapy, phonocardiograms showing no pericardial knock, and apexcardiogram showing normal contour. LLSB = lower left sternal border.

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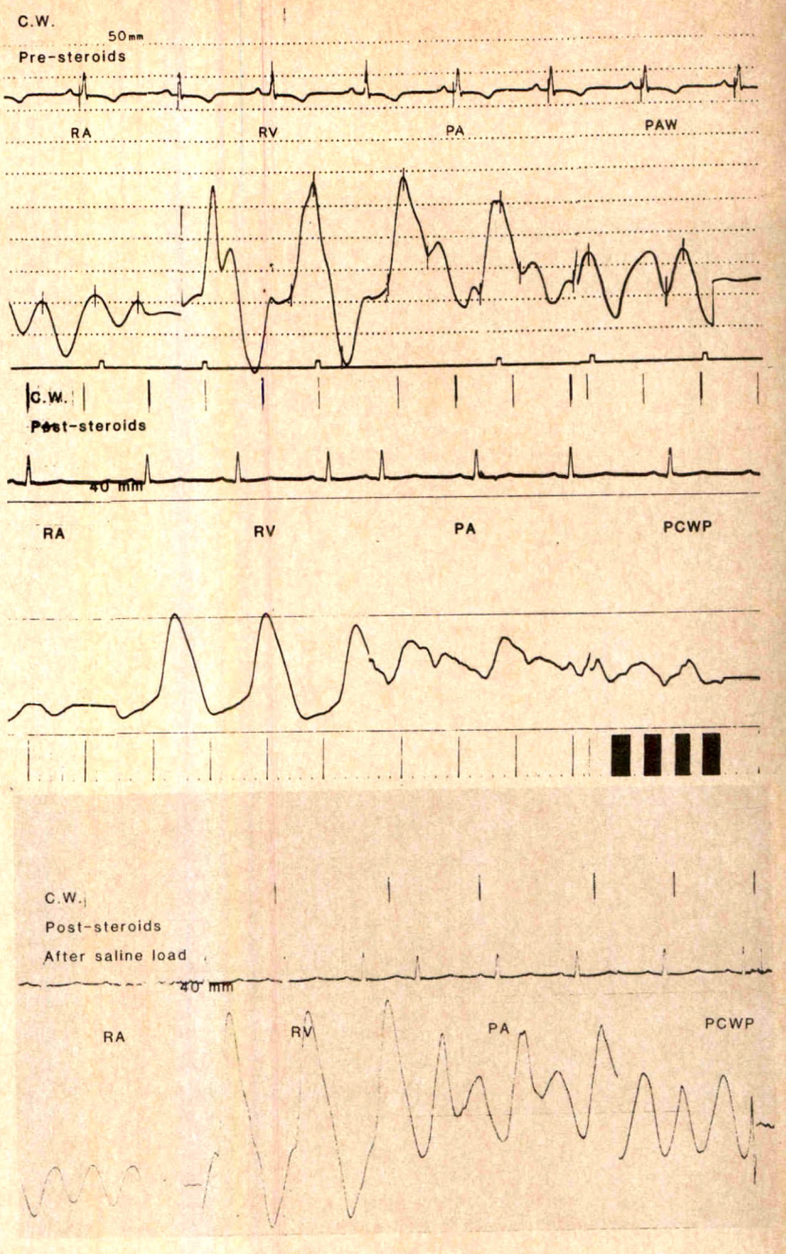

FIGURE 2. Patient CW. **Top,** before steroid therapy, pressure tracings show diastolic plateau and square-root sign. **Center,** after steroid therapy, absence of diastolic plateau and normal right ventricular pressure tracing. **Bottom,** after steroid therapy and saline loading, elevated pressures without contours suggestive of constriction. PA = pulmonary arterial pressure; PCWP = pulmonary arterial wedge pressure; RA = right atrial pressure; RV = right ventricular pressure.

megaly. No pulsus paradoxus, jugular venous distention, pericardial knock, or edema was present. Echocardiography showed a normal functioning mitral prosthesis and no pericardial effusion. Right-sided cardiac catheterization revealed a diastolic plateau of 22 mm Hg with a square-root sign in the right ventricular tracing. The patient was treated with prednisone, 60 mg daily, for 5 days, and then 30 mg daily for 2 weeks. The dose was then tapered over a 4-week period. Repeat right-sided cardiac catheterization 10 days after therapy was initiated showed normal pressures with resolution of the diastolic plateau and square root sign. Symptoms resolved after 2 weeks of therapy. Three years after surgery, there were no signs or symptoms of constriction.

CW, a 45-year-old white man, underwent 3-vessel coronary bypass grafting in August 1979. Surgery was complicated by the postpericardiotomy syndrome. An effusion was noted on echocardiography. Symptoms and effusion resolved with tapering steroid doses in the 2 weeks after surgery. Five weeks after surgery, he had fatigue, chest pain atypical for angina, dyspnea on exertion, and dizziness. Examination revealed jugular venous distention, Kussmaul's sign, a loud pericardial knock, hepatomegaly, and edema. No pulsus paradoxus or pericardial friction rub were present. Echocardiography showed paradoxical septal motion, but no pericardial effusion. Right-sided cardiac catheterization revealed a diastolic plateau with a square-root sign in the pressure tracing (Fig. 2, top). The patient was treated with prednisone, 20 mg twice daily, for 5 weeks. The dose was then tapered over a 4-week period with resolution of symptoms and signs. Recurrent angina led to cardiac catheterization in April 1982, which revealed normal right-sided pressures and contours (Fig. 2, center). After an infusion of 1,000 ml of normal saline solution over 8 minutes for evaluation of occult constriction,[8]

pressures increased, but showed no contours or plateau suggestive of constriction (Fig. 2, bottom). All grafts were patent, but there was progression of native disease, which is being managed medically. Three years after surgery there were no signs or symptoms of a constrictive process.

Discussion

Various causes of postoperative constrictive pericarditis have been proposed,[2,5,6] but no common factor has been identified. As pointed out by others,[3,6] it is probably a combination of factors that result in postoperative constrictive pericarditis. In 17 cases in which the pericardium has been examined at surgery[1,2,4–7] or necropsy,[1,3] most revealed a thick, fibrous adherent pericardium. However, in 1 case[5] there were several adhesions without obliteration of the pericardial space, and less scarring of the pericardium than in the other 2 patients. The investigators suggested that the spectrum of constrictive pericarditis may be broad, with fibrosis being the final stage.

Except for surgery, no therapy for constrictive pericarditis has been reported. Since our patients were stable and since inflammation is implicated in postoperative constrictive pericarditis, we considered a trial of high-dose corticosteroids to be a reasonable intervention. Our patients probably had an early form of a constricting process such as the surgical case just cited.[5] One would not expect a patient with a completed fibrous process to respond to steroids.

Acknowledgment: We thank Roberta Jackson for typing the manuscript.

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LETTERS*

FUNCTIONAL CONSEQUENCES OF RIGHT CORONARY ARTERY ORIGINATING FROM LEFT SINUS OF VALSALVA

We read with interest the report by Roberts et al[1] dealing with the functional consequences of the right coronary artery (RCA) aberrantly originating from the left sinus of Valsalva. The authors' own data and those cited indicate that "origin of the RCA from the left sinus may produce cardiac dysfunction that can be fatal." The authors suggest that the mechanism of flow impairment in the aberrant RCA may be either the diminished flow consequent to the "slit like" origin of the aberrant ostium which becomes even more narrowed during exercise-induced dilatation of the pulmonary trunk and aorta, or the compression ("squeezing") of the anomalous RCA between the aorta and the pulmonary trunk.[2,3]

The latter possibility was challenged already by earlier investigators, mainly because such a phenomenon was never found during coronary arteriography[4–6] or in experimental models.[7] This hypothesis, however, seems to have had its proof in our recent demonstration in a patient of cyclic systolic compression of an aberrant RCA originating from the left sinus of Valsalva (Figure 1).[8] The decrease in the lumen of the RCA at its portion coursing between the great arteries during systole seems to give angiographic support to the theory of "squeezing." However, this finding does not exclude the presence of further mechanisms which may play an additional role in decreasing the flow in the aberrant vessel.

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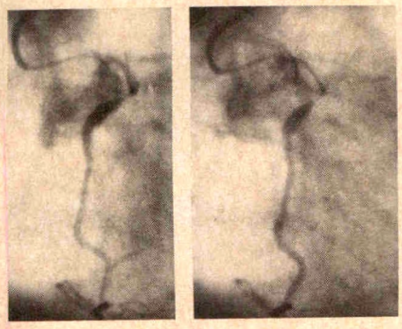

FIGURE 1. Selective injection into the right coronary artery in the right anterior oblique position in diastole (**left**). The portion of the artery coursing between the aorta and pulmonary trunk is dilated. **Right,** same injection and position in systole. The portion of the artery coursing between the aorta and pulmonary trunk is narrowed.

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6. **Baltaxe HA, Wixson D.** The incidence of congenital anomalies of the coronary arteries in the adult population. Radiology 1977;122:47–52.
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* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

SENSITIVITY AND SPECIFICITY OF M-MODE ECHOCARDIOGRAPHIC SIGNS OF MITRAL VALVE PROLAPSE

The report by Haikal et al[1] makes an important contribution in reference to the incidence of different M-mode echocardiographic patterns associated with a nonejection systolic click. The goal of the study was to assign a discriminating statistical value to the sensitivity and specificity of those echocardiographic signs and patterns. At present, there is no uniform agreement on what constitutes a diagnostic standard for the identification of mitral valve prolapse (MVP). It is well known that some patients have a systolic click with or without a murmur, with no evidence of MVP on the echocardiogram. Therefore, any "diagnostic" finding that is being put on the testing bench of scientific analysis for validation needs to be compared and weighed against another standard. That is where the design of the study appears faulty. Sensitivity and specificity simply reflect the capability of detecting a true-positive or excluding a false-positive test result. To make such a statement about specificity or sensitivity, it is mandatory to be able to determine a true-positive test result with a significant degree of certainty. The group from Missouri used a hypothesis that is not universally proven, which is that a systolic click moving in the cardiac cycle with different maneuvers, with or without a murmur, represents or is equivalent to MVP. In the report by Haikal it is not mentioned whether 2-dimensional examination or angiography was performed or used for comparison purposes. The fact that the mid-systolic click was auscultated by 3 independent observers only ascertains the presence of such a finding but does not prove the coexistence of MVP. In that setting the specificity and sensitivity cannot be safely determined.

Edgardo H. Bianchi, MD
Jacksonville, North Carolina

1. **Haikal M, Alpert MA, Whiting RB, Ahmad M, Kelly D.** Sensitivity and specificity of M-mode echocardiographic signs of mitral value prolapse. Am J Cardiol 1982;50:185–190.

REPLY: We agree that nonejection clicks are not specific for MVP. Indeed, such clicks have been described in patients with hypertrophic cardiomyopathy,[1] calcified right atrial myxoma,[2] ventricular septal defect with and without aneurysm of the ventricular septum,[3] and left-sided pneumothorax.[4] In each of these cases the systolic click was nonmobile. In contradistinction, each patient in our study diagnosed as having MVP demonstrated a *mobile* mid-systolic click. Furthermore, the presence of hypertrophic cardiomyopathy, atrial myxoma, ventricular septal defect or aneurysm, and pneumothorax was excluded by echocardiography and chest X-ray. Thus, within the conditions of our study, the mobile nonejection systolic click was a reasonable diagnostic standard for MVP. That nonejection systolic clicks may occasionally occur in the absence of M-mode echocardiographic evidence of MVP can be attributed to the limitations of this technique in viewing mitral valve motion. In his letter, Dr. Bianchi suggests that left ventricular angiography may be a more suitable diagnostic standard for MVP. However, most studies seeking to establish angiographic criteria for MVP have employed the nonejection systolic click with or without late systolic murmur (confirmed by auscultation or phonocardiography) as a diagnostic standard.[5] Also, recent studies have demonstrated marked intra- and interobserver variability in the angiographic diagnosis of MVP[6] thus casting doubt on the usefulness of this technique as a diagnostic standard. Two-dimensional echocardiography may prove to be the most useful method of all for detecting MVP. But to date there have been no large studies comparing the 2-Dimensional echocardiograms of patients with MVP with those of normal subjects. Thus, it seems premature to identify 2-dimensional echocardiography as the diagnostic standard for MVP.

Martin A. Alpert, MD
Richard B. Whiting, MD
Maged Haikal, MD
Columbia, Missouri

1. **Sze, KC, Shah, PM.** Pseudoejection sound in hypertrophic subaortic stenosis. Circulation 1976;54:504–509.
2. **Martin CE, Hufnagel CA, deLeon AC.** Calcified atrial myxoma: diagnostic non-mobile significance of the "systolic tumor sound" in a case presenting as tricuspid insufficiency. Am Heart J 1969;78:245–250.
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4. **Roelandt J, Willems J, Vander Hauwert LG, de Geest H.** Clicks and sounds in left sided pneumothorax. Dis Chest 1969;56:31–36.
5. **Ranganathan N, Silver MD, Robinson TI, Wilson JK.** Idiopathic prolapsed mitral leaflet syndrome. Angiographic-clinical correlations. Circulation 1976;54:707–715.
6. **Kennett JD, Rust PF, Martin RH, Parker BM, Watson LE.** Observer variation in the angiographic diagnosis of mitral valve prolapse. Chest 1981;79:146–150.

The report by Haikal et al[1] quoted a 4% prevalence of mitral valve prolapse (MVP) in the general population. In our opinion, that is an underestimation and the range should be between 5 and 10%,[2,3] as indeed reflected by the authors' own findings of 11 MVP subjects among 100 asymptomatic volunteers.

We agree with the authors that because of the high prevalence of MVP and its clinical implications, the diagnostic criteria used should possess "reasonable sensitivity and a high degree of specificity." We disagree with the reported specificity of the last 3 echocardiographic criteria tested in Table I, except thickening of the mitral leaflets. According to the authors' data, the specificity of multiple parallel systolic echoes, the increased early diastolic excursion of anterior mitral leaflet, and the abutment of the anterior mitral leaflet against the ventricular septum should be 22, 58, and 77%, respectively, instead of the reported 78, 42, and 23%.[1]

E. G. Abinader
D. Sharif
S. Malouf
Haifa, Israel

1. **Haikal M, Alpert MA, Whiting RB, Ahmad M, Kelly D.** Sensitivity and specificity of M-mode echocardiographic signs of mitral valve prolapse. Am J Cardiol 1982;50:185–190.
2. **Devereaux RB, Perloff JK, Reichek N, Josephson MD.** Mitral valve prolapse. Circulation 1976;54:3–14.
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4. **Crawley IS, Morris DC, Silverman BD.** Valvular heart disease. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart. 4th ed. New York, McGraw-Hill, 1978;992.

INTRANODAL CONDUCTION PATHWAYS IN COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

In the Symposium on Postoperative Congenital Heart Disease in Adults in the September 1982 issue of the Journal, I was particularly interested in the reports on conduction tissues by Barati and Lev[1] and Vetter and Horowitz.[2] There appears to be a highly significant difference in their conclusions on the results of surgery for complete transposition. On page 595, Vetter and Horowitz, quoting the important study of Wittig et al,[3] state that damage to the preferential intranodal conduction pathways "was sufficient to compromise activation of the A-V node and produce junctional rhythm." However, on page 586, Bharati and Lev state, "With time, this pathway may become fibrotic, yielding A-V block." The latter finding, if true, is of considerable significance, yet Bharati and Lev do not give the source of their data. Is this a speculative comment, or have they firm evidence to confirm this prognostication?

Robert H. Anderson, MD
London, United Kingdom

1. **Bharati S, Lev M.** Sequelae of atriotomy and ventriculotomy on the endocardium conduction system and coronary arteries. Am J Cardiol 1982;50:580–587.
2. **Vetter VL, Horowitz LN.** Electrophysiologic residua and sequelae of surgery for congenital heart defects. Am J Cardiol 1982;50:581–601.
3. **Wittig JH, DeLeval MR, Stark J, Castaneda A.** Intraoperative mapping of atrial activation before, during & after the Mustard operation. J Thorac Cardiovasc Surg 1977;73:1–13.

REPLY: In response to the question of whether disruption of the pathways between the sinoatrial and atrioventricular (AV) nodes will result in some form of AV dissociation, we refer to an earlier report of ours[1]: In case 1 there was sinus rhythm alternating with junctional rhythm in the last year of the child's life. There was also first-degree AV block. Pathologically, we found that only part of the superior preferential pathway remained, and it was interrupted in part by sutures. In case 2, 2 months before death, there was first-degree AV block which progressed to second-degree with 2:1 conduction alternating with a junctional rhythm with AV dissociation. Pathologically, the superior and middle preferential pathways were replaced by fibrous tissue and by the pericardial prosthesis. The inferior preferential pathway had been removed surgically.

Thus, our work demonstrates that operation on the conduction pathways may be important in preventing arrhythmias and various degrees of AV block. Both cases also revealed that the approaches to the sinoatrial and the AV node were markedly fibrosed. In case 1 the sinoatrial node was interrupted by sutures and in case 2 it was considerably fibrosed. Therefore, we concluded the following: "... Our work does not determine the importance of preserving the internodal pathways, which were also found to be disrupted in our cases. In this regard, the work of Holsinger and associates[2] is pertinent. These workers found in their experiments on dogs that the integrity of at least the superior atrial preferential pathway was important in atrial conduction. When the posterior internodal pathway was divided, there was no change in the PR time. Dividing the middle pathway still did not cause a delay in atrial conduction. However, division of the remaining anterior pathway did produce a delay in atrial conduction. When the 3 pathways were interrupted, nodal rhythm occurred in 7 of 10 dogs. Similar findings were obtained by Waldo,[3] Pereira Leite,[4] and their co-workers. Thus experimental evidence suggests that in addition to retaining the integrity of the approaches to the SA and AV nodes, it is advisable to retain the superior internodal pathway in the Mustard procedure." [5,6]

Saroja Bharati, MD
Chicago, Illinois

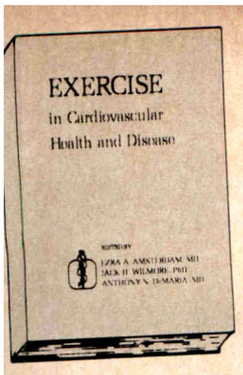
1. **Bharati S, Molthan ME, Veasy LG, Lev M.** Conduction system in two cases of sudden death two years after the Mustard procedure. J Thorac Cardiovasc Surg 1979;77:101–108.
2. **Holsinger JW Jr., Wallace AG, Sealy WC.** The identification and surgical significance of the atrial internodal conduction tracts. Ann Surg 1968;167:447–453.
3. **Waldo AL, Bush HL Jr., Gelband H, Zorn GL Jr., Vitikainen KJ, Hoffman BF.** Effects on the canine P wave of discrete lesions in the specialized atrial tracts. Circ Res 1971;29:452–467.
4. **Pereira Leite P, Borelli V, de Brito FS, Andretto R.** Experimental selective blocks of the internodal conduction pathways in the dog. Rev Fac Med Vet Zootec Univ S Paulo 1976;13:421–458.
5. **Isaacson R, Titus JL, Merideth J, Feldt RH, McGoon DC.** Apparent interruption of atrial conduction pathways after surgical repair of transposition of great arteries. Am J Cardiol 1972;30:533–535.
6. **Waldo AL, Krongrad E, Bowmann FO, Kaiser GA, Husson GS, Malm JR.** Electrophysiological considerations during total repair of transposition of the great vessels. Circulation 1972;46:Suppl II:II-34.

TERM OBLITERATION OBSESSION (TOO)

The manifestation of a new disease always excites interest, and we draw your attention to a hitherto undescribed syndrome: term obliteration obsession (TOO). TOO is characterized by an overwhelming compulsion to deliberately abbreviate real nouns (DARN), and indeed any other word which comes within the sphere of this strange and acquired Machiavellian malady. The following examples were culled at random from current reports: ALAD for abnormal left axis deviation; AWP for alternating Wenckebach phenomenon; CPB for cardiopulmonary bypass; CSRT for corrected sinoatrial recovery time; SNCL for sinus node cycle length; RHR for resting heart rate; IHR for intrinsic heart rate; and IHRo for observed intrinsic heart rate. TOO presupposes immediate decipherment (PID) so that understanding (STU) is possible. TOO is thus specifically designed to frustrate orderly reading (FOR), thereby causing a predictable response: worry over redundant diminutive stupidity (WORDS). An unexpected and remarkable feature of TOO is that it rarely, if ever, affects single words, 2 being the minimum requirement for TOO. This exception would therefore seem to be the obvious starting point for further research. TOO is random, disorderly, illogical, unpredictable, and to no purpose. The nondifferentiating character of the disease is evident from the fact that the same acronym may be used for different conditions: for example, MI for myocardial infarction as well as mitral insufficiency. TOO should therefore be regarded as a primitive undifferentiated lingering malignant disease. TOO is endemic in the United States and is especially rampant among cardiologists, having indeed reached epidemic proportions. Electrophysiologists, in particular, are very prone to this affliction. Mortality is uncommon but morbidity profound. There is no known treatment.

The features of this syndrome may thus be presented succinctly as follows: Term obliteration obsession deliberately abbreviates real nouns so that understanding presupposes immediate decipherment, frustrating orderly reading by worrying over redundant diminutive stupidity. Or, to TOO it so that it is even more succinct: TOO DARN STU PID FOR WORDS.

Leo Schamroth, MD, DSc, FRCP, FRS
David Blumsohn, MBBCh, Dip Med
Johannesburg, South Africa



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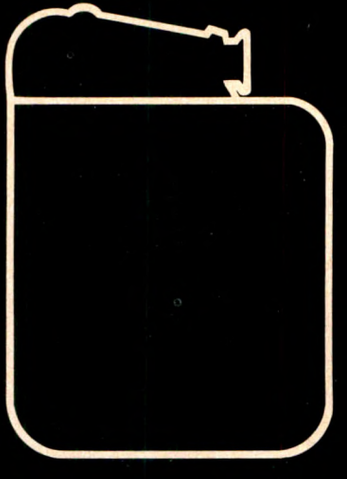

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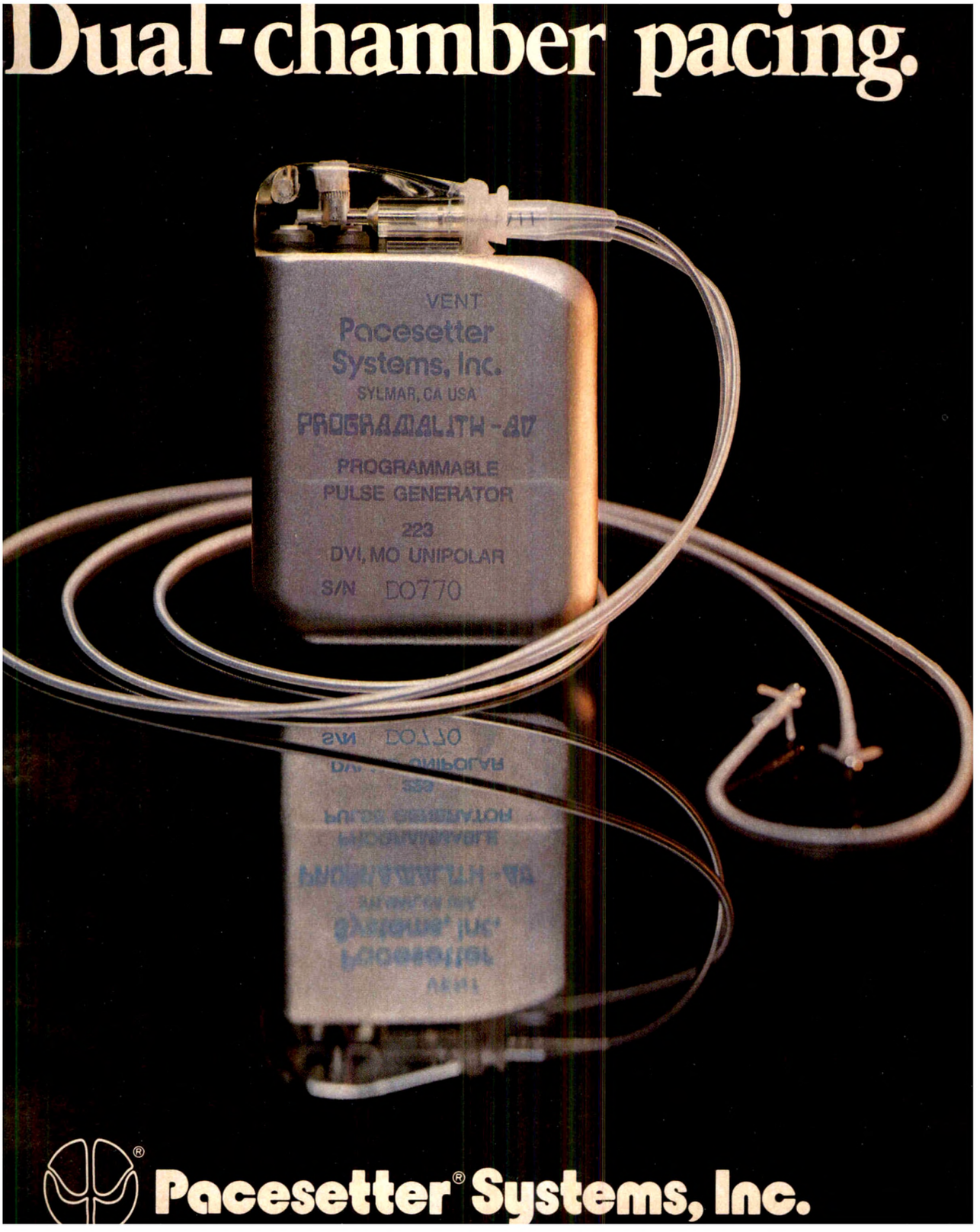

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Measured Telemetry Values Retrieved Additionally with 398E Programmer:	Rate, Vtr. Pulse Current, Vtr. Pulse Voltage, Vtr. Pulse Energy, Vtr. Pulse Charge, Battery Voltage, A-V Delay	
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Capacity:		
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Voltage	2.8 V	
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Volume	30 cc	
Density	2.3 gm/cc (Approximately)	
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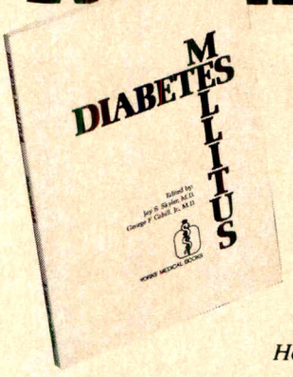

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Mechanism I: Nitrates reduce myocardial oxygen requirement by acting on systemic circulation. Their vasodilator action decreases venous return and systemic arterial resistance, thus improving the balance between the need and supply of oxygen. Reduction in the myocardial oxygen requirement appears to be the major action of nitrates in relieving typical angina. However, selective dilatation of large coronary vessels by nitrates may be the primary mechanism by which they benefit patients with angina due to coronary spasm.[1]

Mechanism II: In contrast, beta-blockers block the beta receptor sites in the heart itself. They work by reducing the heart rate and the force of contraction, thereby lowering oxygen demand. In addition to cardiac output and heart rate, blood pressure is also decreased.

Beta-blockers may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction.

■ diminished side effects: some of the negative aspects of the effects of each drug are reduced. For example, concomitant nitrates oppose the increased ventricular size, filling pressure, and end-diastolic pressure caused by beta-adrenergic antagonists.[1]

The effects of NITROSTAT® SR and a beta-blocker are complementary. The result can be improved therapy for angina prophylaxis.

■ all day and all night prophylactic action with just two or three daily doses*

How Supplied: 2.5-mg and 6.5-mg strengths, in bottles of 60 and 100 capsules. Also, 9.0-mg strength, in bottles of 60 capsules.

Please see next page for brief summary of prescribing information.

NITROSTAT® SR...Backed by the experience and reputation of PARKE-DAVIS

*Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows. "Possibly" effective: For the management, prophylaxis or treatment of anginal attacks. Final classification of the less-than-effective indication requires further investigation.

REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS and Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

NITROSTAT® SR CAPSULES
(nitroglycerin capsules)
SUSTAINED RELEASE

Before prescribing, please see full prescribing information. A Brief Summary follows:

INDICATION: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indication as follows.

"Possibly" effective: For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS:
Acute or recent myocardial infarction, severe anemia, closed-angle glaucoma, postural hypotension, increased intracranial pressure and idiosyncrasy to the drug.

WARNINGS:
Capsules must be swallowed. FOR ORAL, NOT SUBLINGUAL USE. Nitrostat SR Capsules are not intended for immediate relief of anginal attacks.

PRECAUTIONS:
Intraocular pressure may be increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug and cross-tolerance to other organic nitrites and nitrates may occur. If blurring of vision, dryness of mouth or lack of benefit occurs, the drug should be discontinued.

ADVERSE REACTIONS:
Severe and persistent headaches, cutaneous flushing, dizziness and weakness. Occasionally, drug rash or exfoliative dermatitis, and nausea and vomiting may occur; these responses may disappear with a decrease in dosage. Adverse effects are enhanced by ingestion of alcohol, which appears to increase absorption from the gastrointestinal tract.

DOSAGE AND ADMINISTRATION:
Administer the smallest effective dose 2 or 3 times daily, at 8- to 12-hour intervals, unless clinical response suggests a different regimen. Discontinue if not effective. 0883G010

Manufactured by:
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St. Louis, Missouri 63144

Distributed by
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Morris Plains, New Jersey 07950

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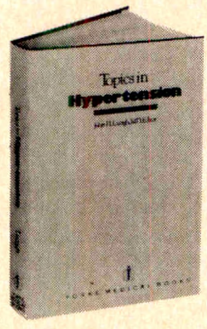

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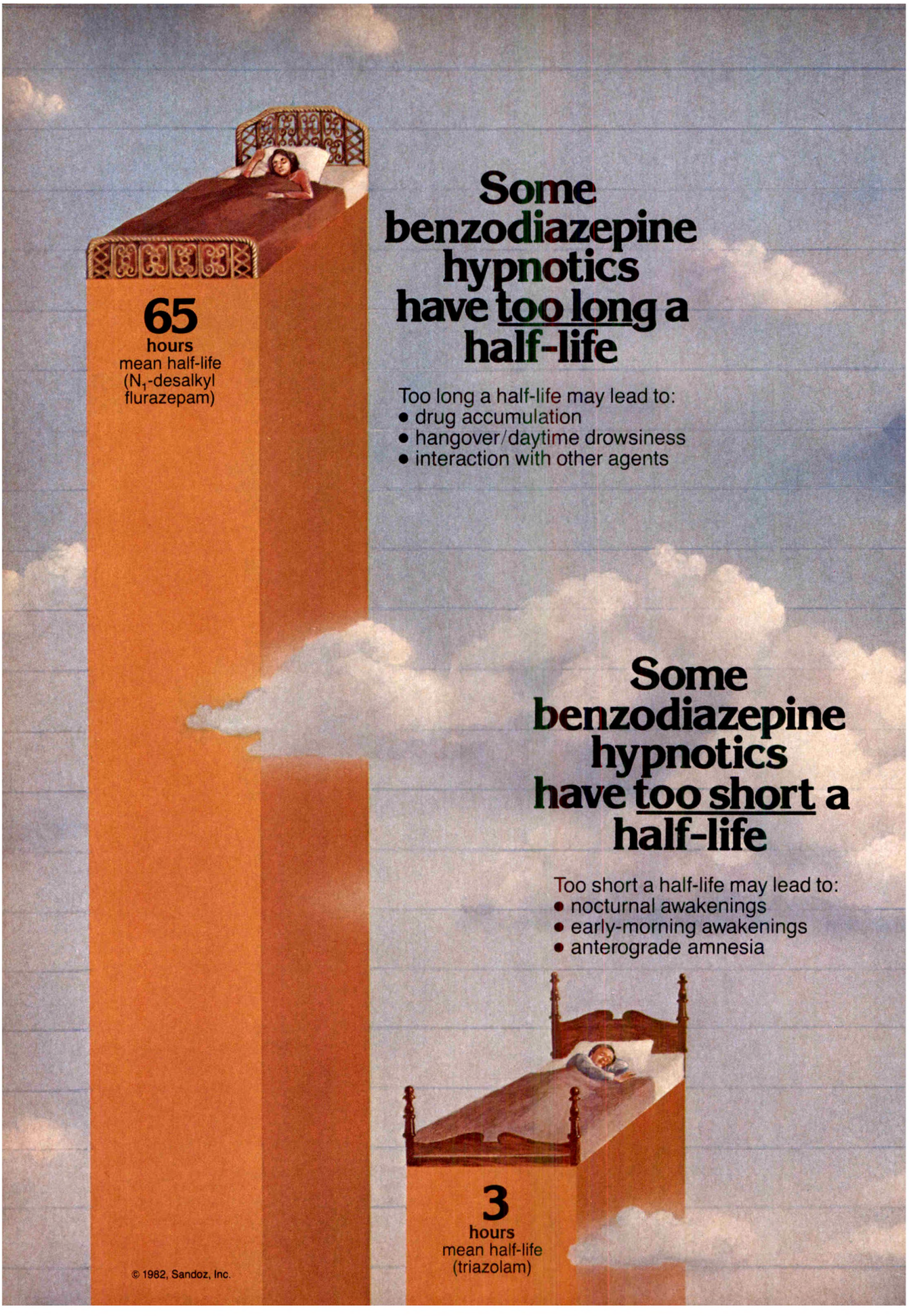
65
hours
mean half-life
(N_1-desalkyl
flurazepam)
Some benzodiazepine hypnotics have too long a half-life
Too long a half-life may lead to:
• drug accumulation
• hangover/daytime drowsiness
• interaction with other agents
Some benzodiazepine hypnotics have too short a half-life
Too short a half-life may lead to:
• nocturnal awakenings
• early-morning awakenings
• anterograde amnesia
3
hours
mean half-life
(triazolam)
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Restful sleep, alert awakening

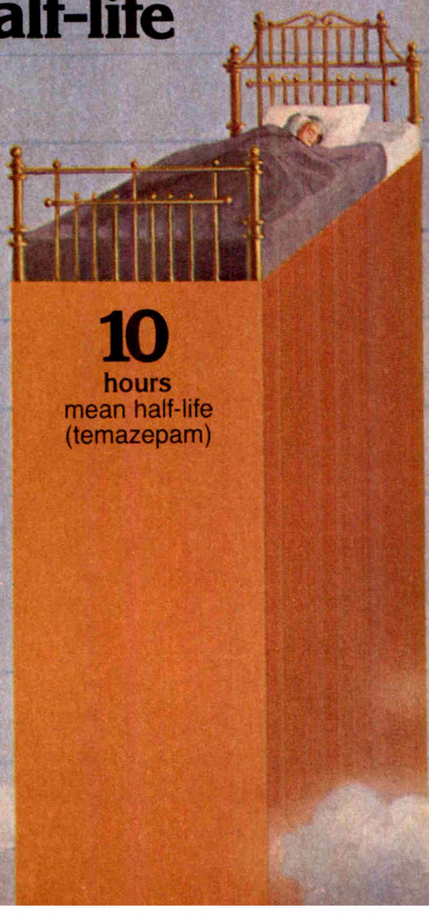
RESTORIL®

C IV

15 mg
30 mg
capsules

(temazepam)

RESTORIL®
(temazepam)
has an appropriate half-life



A half-life (mean of 10 hours) that parallels normal sleep time:

- patient gets 7-8 hours sleep
- most medication gone by morning
- patient awakes alert and refreshed
- minimal side effects
- insignificant accumulation

Please see brief summary of prescribing information on next page.

Restful sleep, alert awakening

RESTORIL® (temazepam) 15 mg 30 mg capsules

A more appropriate half-life

One 30-mg capsule, h.s.—*usual adult dosage.*
One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

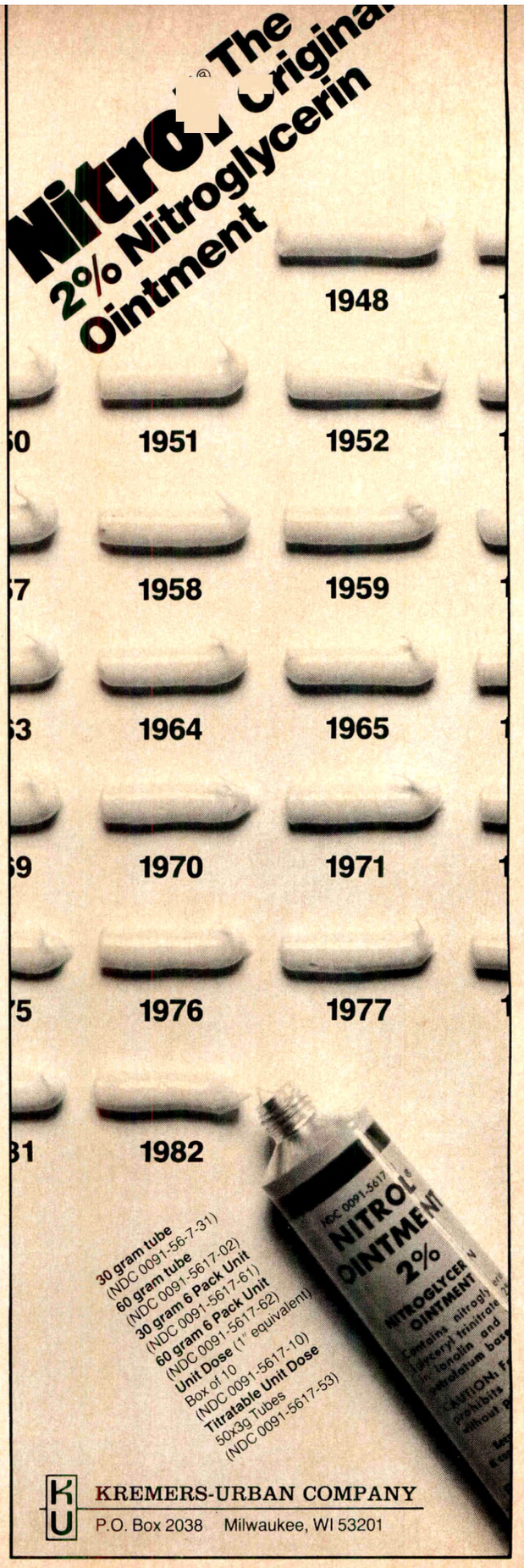
DOSAGE AND ADMINISTRATION: *Adults:* 30 mg usual dosage before retiring; 15 mg may suffice in some. *Elderly and/or debilitated:* 15 mg recommended initially until individual response is determined.

SUPPLIED: Restoril (temazepam) capsules—15 mg maroon and pink, imprinted "RESTORIL 15 mg"; 30 mg, maroon and blue, imprinted "RESTORIL 30 mg". Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous reverse-numbered roll of sealed blisters). (RES-Z2 11/1/81)

Before prescribing, see package insert for full product information.

RES-183-2

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936



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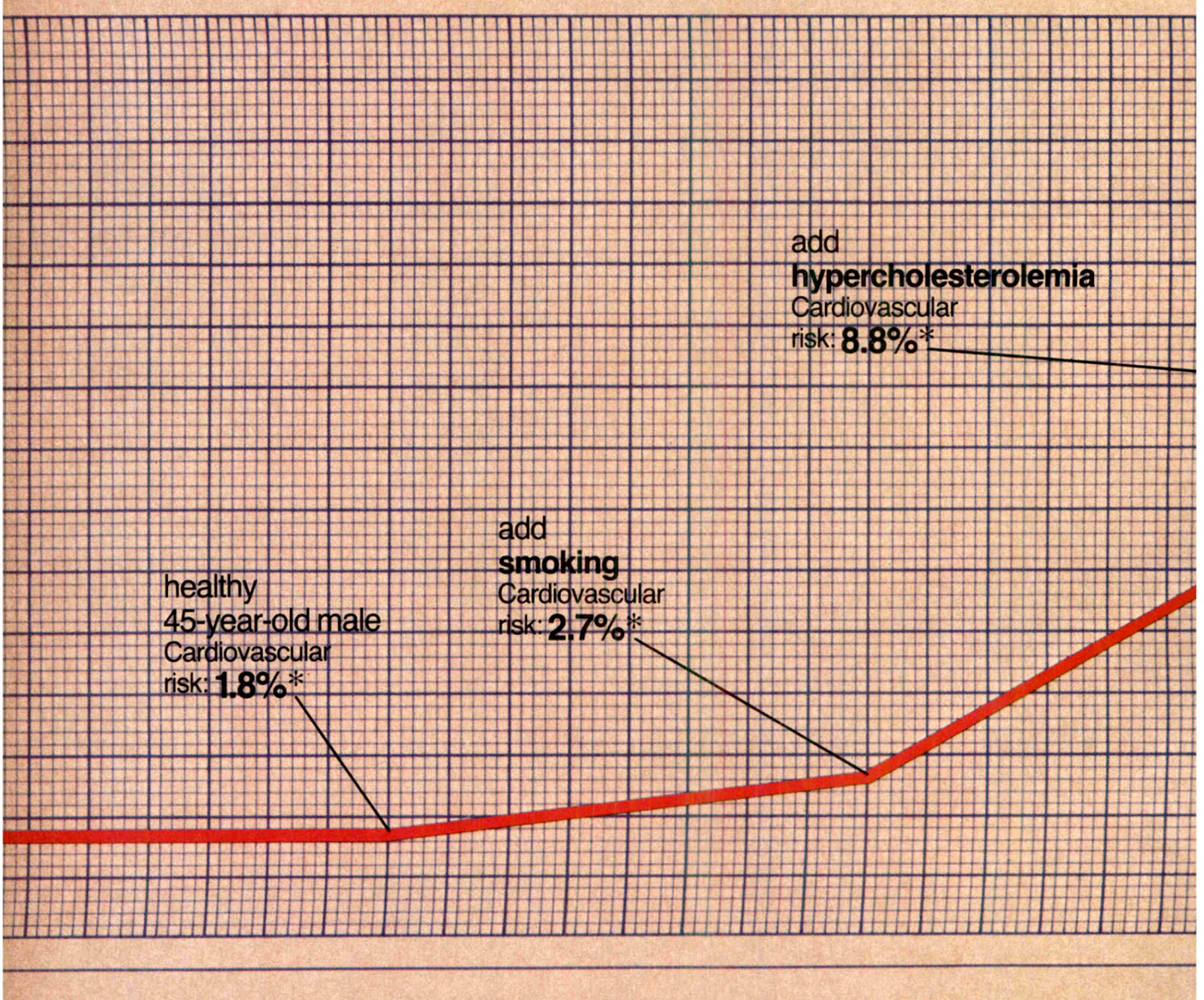
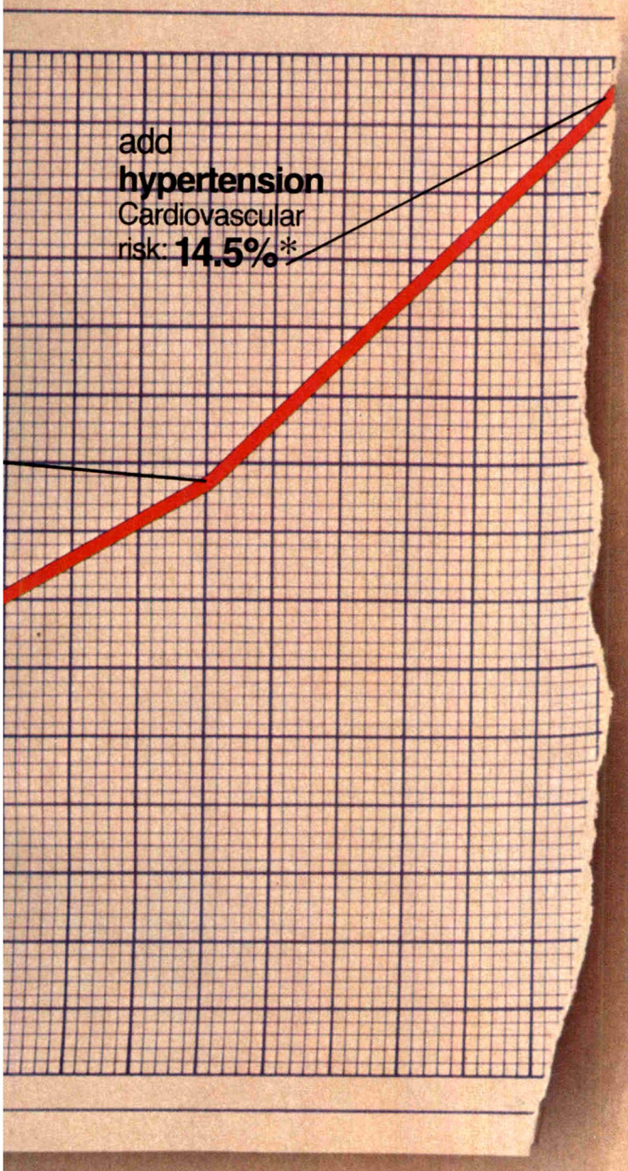


Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

Consider the Risks



- When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

Minipress Effectively Controls Hypertension Without Adverse Effect on Blood Lipids†

- Minipress effectively treats hypertension. Patients have benefited from the effectiveness of Minipress in over 5 years of clinical use in this country.[1-5]
- Minipress has been shown not to have an adverse effect on blood lipids, according to The Oslo Study and other reports.[6-9] Because Minipress lowers high blood pressure and does not produce lipid changes which are potentially atherogenic, it provides your patient with a net reduction in risk.

†Minipress is not indicated for the treatment of hyperlipidemia.

Please see Minipress brief summary on following page.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

© 1982, Pfizer Inc.

Minipress® (prazosin HCl) Capsules 1mg, 2mg, 5mg

B.I.D. Dosage Convenience

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*
INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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CARDIOLOGY: 1982

The Second Issue of the New Annual providing a multidisciplinary approach to the latest, most important information on the state-of-the-art of cardiovascular medicine and surgery

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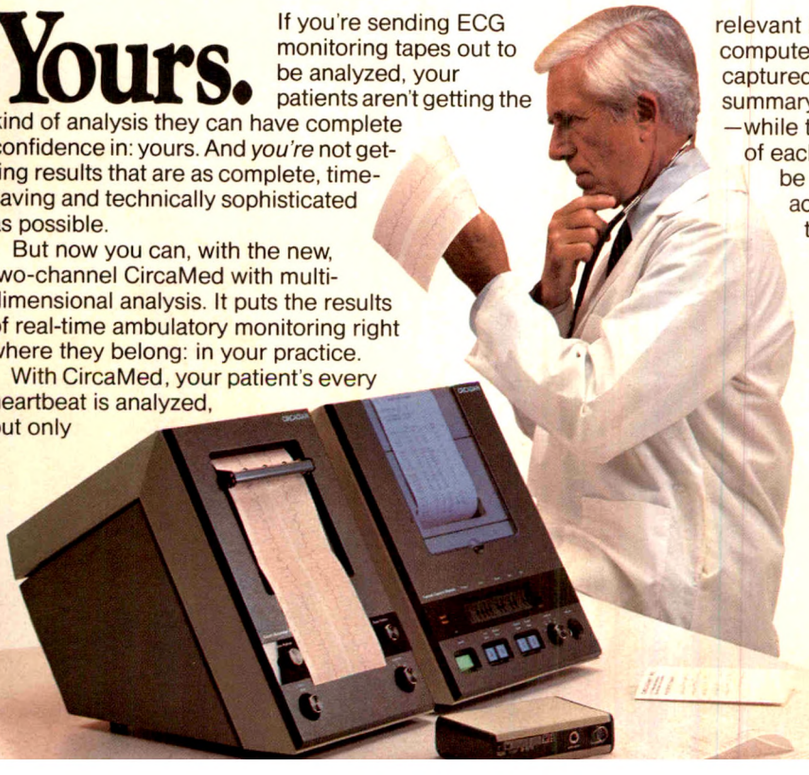

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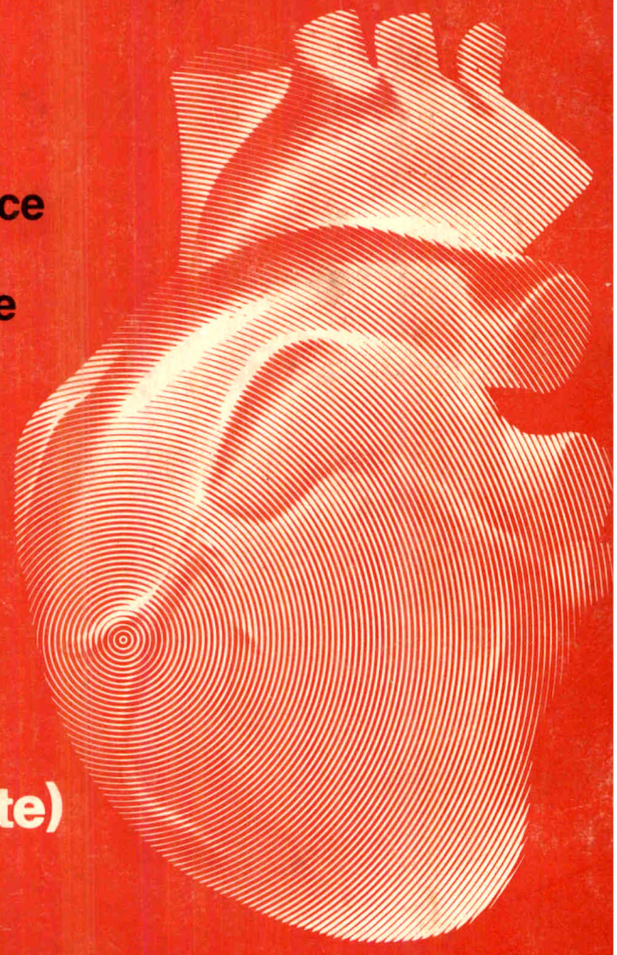

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With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
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PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases whe the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: Th drug should be used with caution due to excretion of the quinidine in breast milk. ADVERS REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/ disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTES TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QR complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricul tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMA TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulo cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, an syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasi blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, nigh blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intens pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episod vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribin Information.

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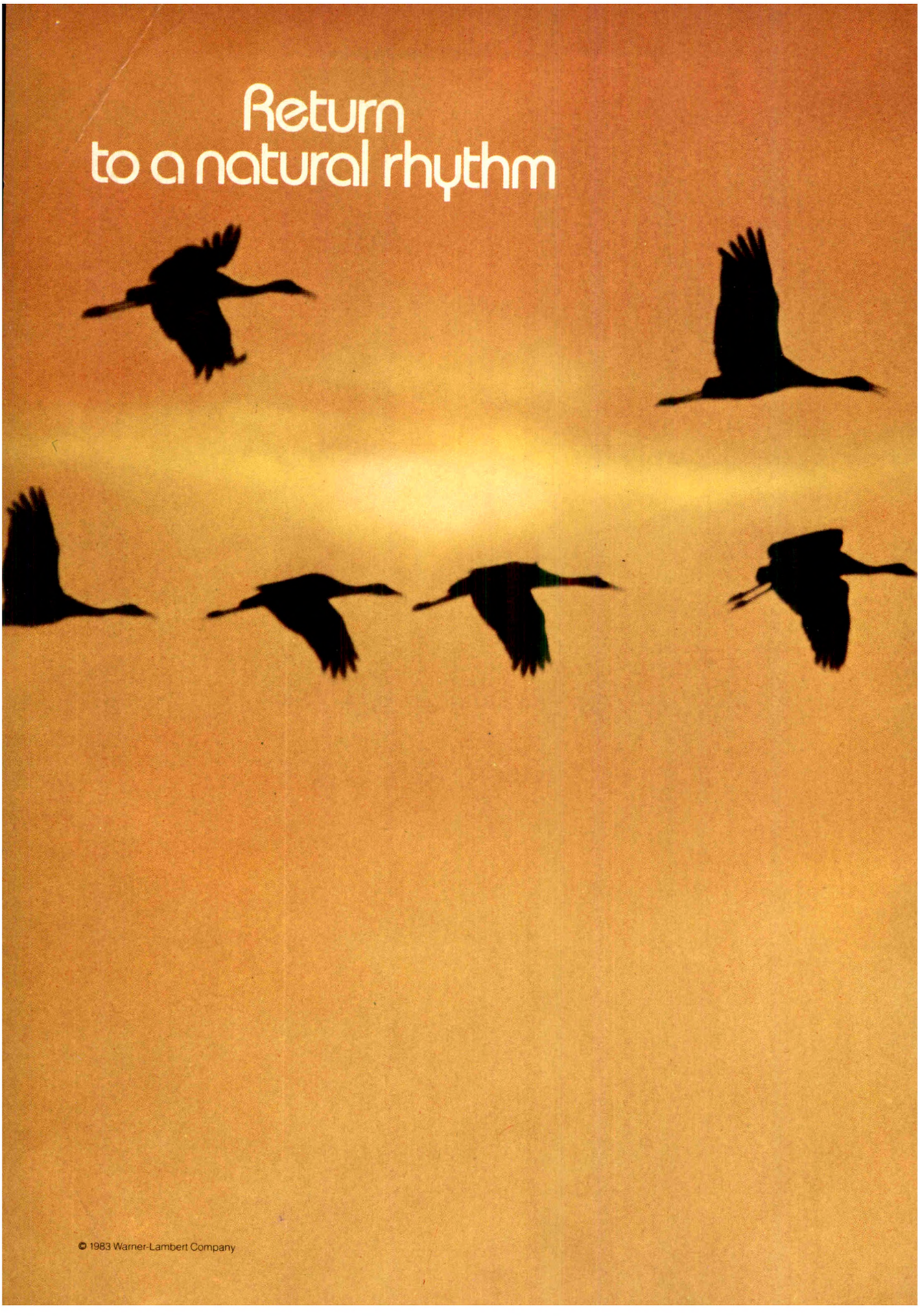

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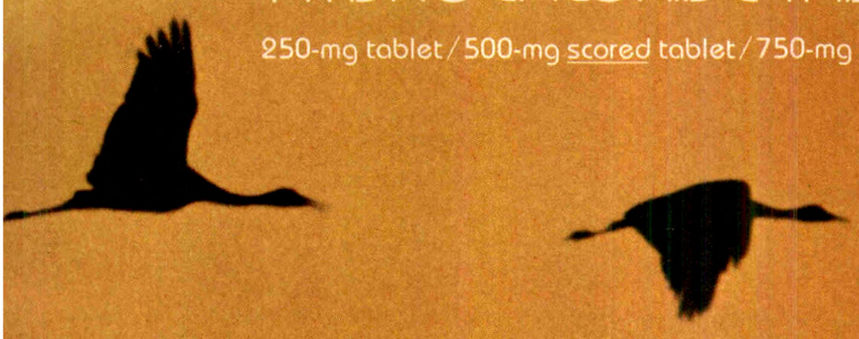

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A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: Procan SR 250 mg (green, film-coated tablet, P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

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Procan SR 750 mg (orange, scored, film-coated tablet, P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).

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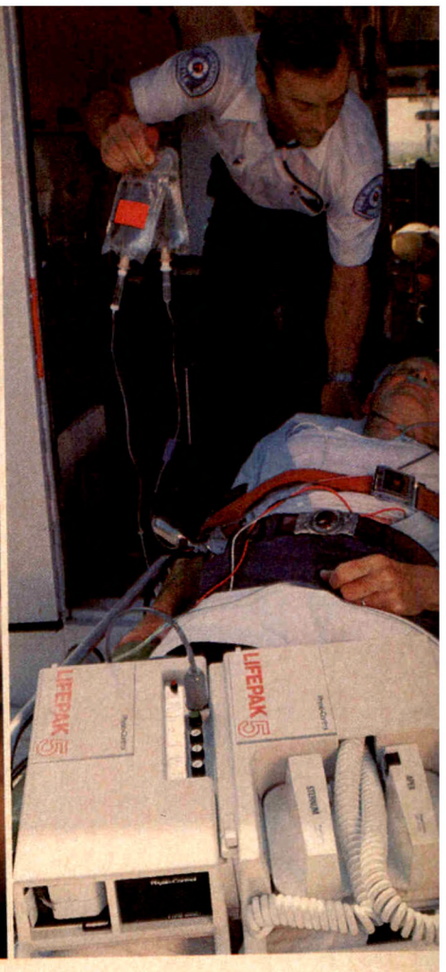

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Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

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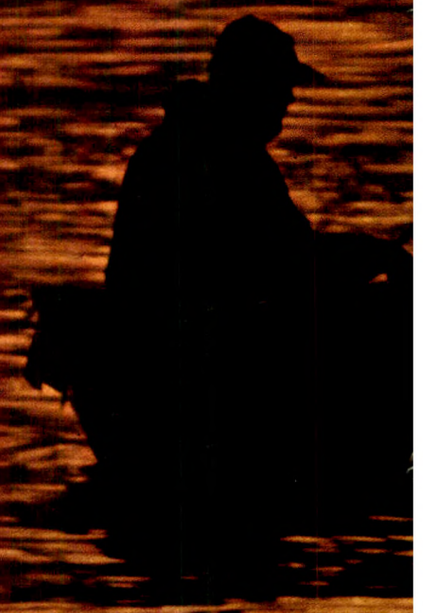

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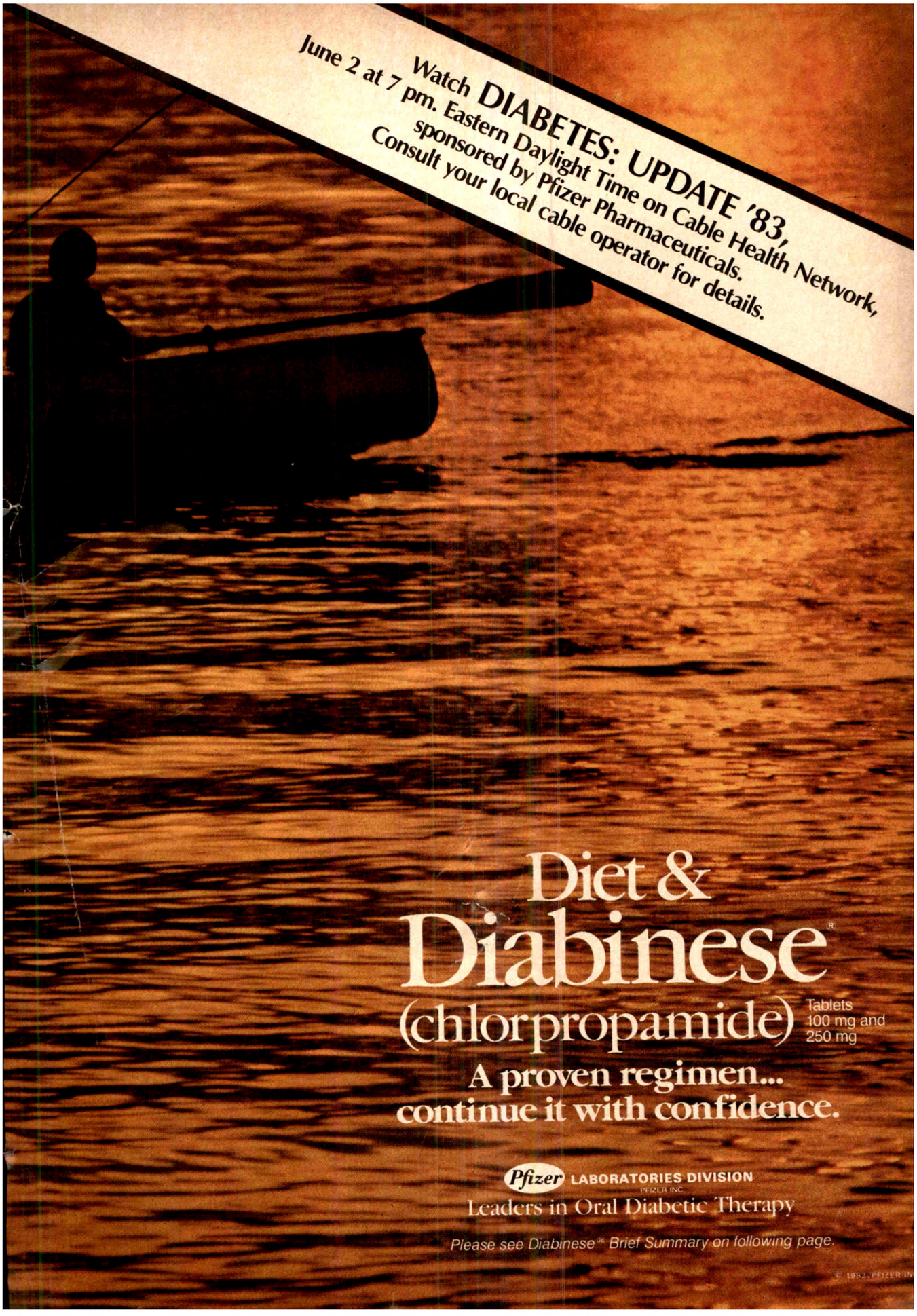
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Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.
Precautions: Use chlorpropamide with caution with barbiturates, in patients with Addison's disease or in those ingesting: alcohol, antibacterial sulfonamides, thiazides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors. Adequate dietary intake should be assured in all patients using Diabinese.
Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HERE, INSULIN IS INDISPENSABLE.
HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED. (SEE ADVERSE REACTIONS.) IN INSTANCES OF CONCOMITANT USE WITH INSULIN, PATIENTS SHOULD BE CAREFULLY MONITORED.
Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, nausea, vomiting and gastrointestinal intolerance; weakness and paresthesias.
Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. They occur characteristically during the first six weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug. The more severe manifestations may require other therapeutic measures, including corticosteroid therapy. Diabinese should be discontinued promptly when the development of sensitivity is suspected.
Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPIENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.
Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.
Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.
BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG REQUIRE CLOSE SUPERVISION FOR A MINIMUM PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.
Rare cases of phototoxic reactions have been reported.
Edema associated with hyponatremia has been infrequently reported. It is usually readily reversible when medication is discontinued.
Dosage: The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally, cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED. The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of Diabinese, in the range of 100 to 125 mg daily.
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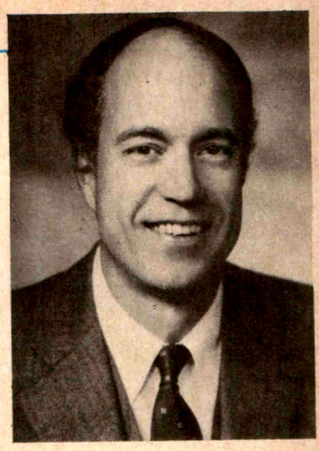


References: A Clue to Scholarship

References are an important part of a manuscript. Their selection is an indicator of the author's knowledge of and regard for work preceding his own, and their accuracy of recording is a clue to the quality of the author's own work. Indeed, their selection and the accuracy of their recording is a clue to the scholarship of the manuscript. This piece examines the process of selecting references, suggests a procedure to record them accurately, and describes the reasons why references are listed as they are in the AJC.

The Selection Process: Some authors tend to support statements in their manuscripts by multiple references, but often when this is done, some references do not support the statement for which they are being used. Other authors provide few references and open themselves to criticism for not giving sufficient credit to their predecessors. Should the initial or latest work on the subject be cited, or simply the present author's previous work on the subject? A clear answer to this question is lacking. A middle course between "too many" and "too few" references appears most reasonable.

A frequent criticism by reviewers of manuscripts is that their work was not cited. Accordingly, the reviewer may feel slighted and may react by being overcritical. Reference to an individual increases the chance, however, that that person will review the manuscript in question. I certainly look at the references cited when deciding to whom I will send a manuscript for review. When reading a published or unpublished paper on which they too have contributed information, many author-readers review the list of references cited. I am reminded of a story regarding 2 prominent present-day authors. William Buckley sent his most recent book to John Kenneth Galbraith, who, upon receiving it, immediately turned to the title page, anticipating a note from his friend Buckley. Finding none, Galbraith turned to the list of references and beside the first citation of one of Galbraith's books, Buckley had written, "Hi, John, Bill."

Manuscripts containing innumerable references are more likely a sign of insecurity than a mark of scholarship. It requires enormous confidence to submit a manuscript devoid of references, but references may not be necessary if the data presented is entirely new. I sometimes see manuscripts with too many references and too little data. That a publication has been read during the preparation of a manuscript is not justification for its being cited as a reference. References, in other words, should not represent a list of publications read by the author—"how much work he (she) did," so to speak. In my own manuscripts, I tend to cite about one-half to two-thirds of the publications I read in preparing the manuscript. References should be carefully selected, the references cited should in general be for quality papers, they should clearly support the statement or comment to which they are attributed; and, just as a good paragraph should have no unnecessary sentences and a good sentence no unnecessary words, a manuscript should have no unnecessary references. Each reference, like each paragraph or sentence, should have a meaningful purpose.

In the Brief Reports section of the AJC, the number of references should be limited to 6 or fewer; in Letters to the Editor, usually to 3 or fewer.

Accuracy of Recording References: Many errors are made in recording references in manuscripts. Examine any 10 references in any medical journal and usually at least 1, often more, will contain an error. Errors in references represent inadequate regard for the work of previous researchers, and I suspect that inaccurately recorded references are found most frequently in manuscripts containing inadequately recorded data. Therefore, as an editor, as well as reader, I carefully examine all references in manuscripts submitted to the AJC. Names are frequently

Continued on page A10

misspelled, initials preceding the last name are often wrong, and "Junior" or "III" occasionally are omitted. Titles often are recorded inaccurately and subtitles frequently are omitted. Volume numbers, page numbers, and year of publication often are erroneously recorded. A major source of error in citing a reference is recording a reference listed in another publication. In this situation, the error recorded in the first listing is propagated in the subsequent publication. The same careful attention should be given to references as is given to other aspects of a manuscript.

The following procedures have proved useful to me in diminishing errors in recording references for my own manuscripts.

1. Each reference initially is recorded on a 3- by 5-inch card and the writing is print rather than script to prevent subsequent misinterpretation when typed. All authors, full title with subtitle, volume, inclusive page numbers, and month and year of publication are recorded on these cards. If a reference is obtained from a previous author's reference list, a notation is made on the card that the original needs to be reviewed. The reason for recording the month of publication is that this ensures review of the original report because month of publication, of course, is not listed in published reference lists. Additionally, recording both the month and year of publication allows chronologic listing of references published in the same year on the same subject.

2. The senior or established author must check references recorded by young or relatively new investigators to ensure accuracy. Some medical institutions have librarians who check the accuracy of recorded references, but this is a luxury afforded by few medical centers or research institutions.

3. References are recorded only from the original publication. To cite a reference from a previously published reference list without checking the original publication is poor research. A medical publication should never be referenced without reading it!

4. References are *typed only once* and that is in final form in the final manuscript directly from the 3- by 5-inch cards on which they were originally recorded. The cards are numbered in pencil in the order in which they will appear. Having each reference on a separate card allows the author to change the order without altering the entire typed format.

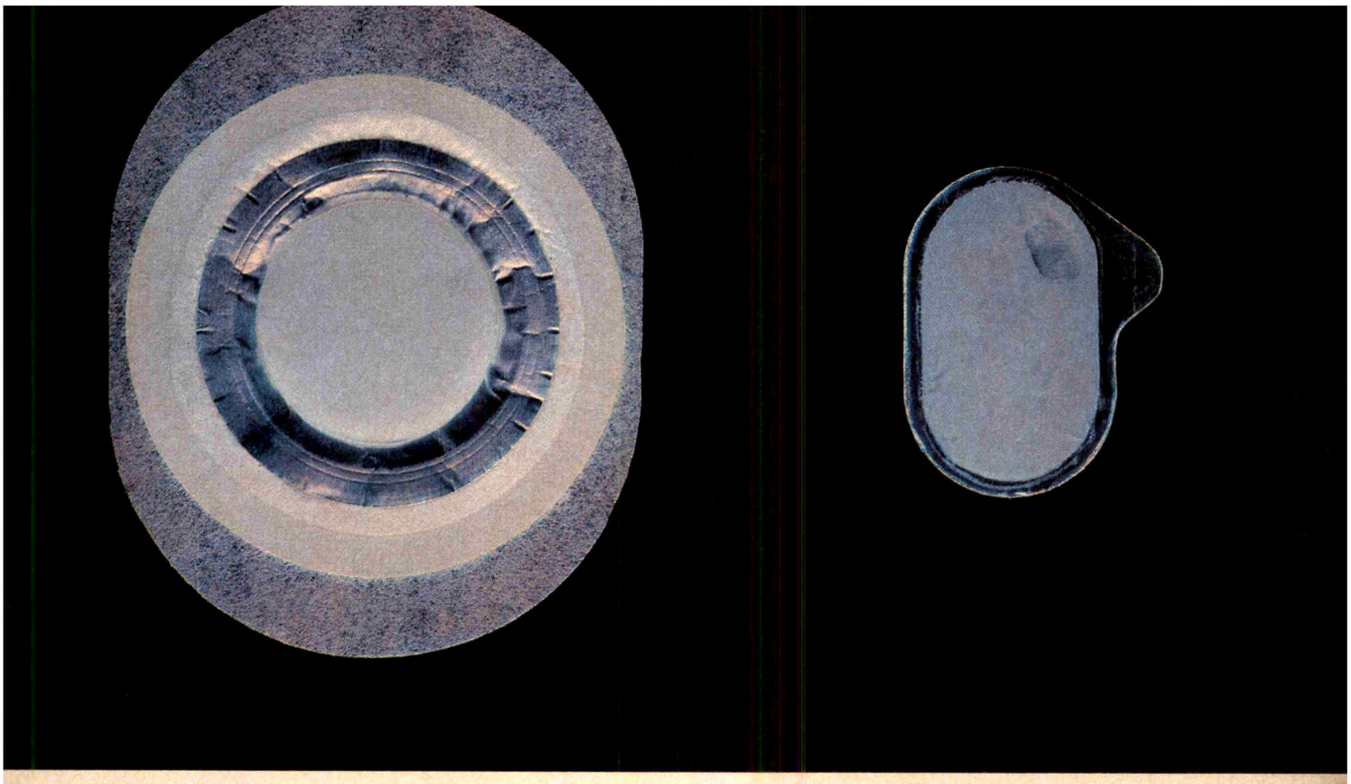
5. The typed list of references is carefully proofed from the original 3- by 5-inch reference cards by the recorder of the references on the cards. This person can read his or her own handwriting better than anyone else. More typographical errors are made in typing references than in any other portion of a manuscript. Therefore, the single typing of references from the original reference cards prevents errors which occur from multiple typings.

6. The references in the galley proofs are again checked against the original 3- by 5-inch reference cards.

Listing of References in the AJC: References listed in the AJC are complete in that the names of *all authors*, *subtitles* as well as primary titles, and *inclusive page numbers* are required. Manuscripts submitted to the AJC with references in another format suggest that the paper has been submitted previously to another journal which rejected it, or that the authors are not sensitive students of medical publications. With text pages at a premium, why are all authors, all titles, and inclusive page numbers required in the AJC? By listing all authors, all titles, and inclusive page numbers (rather than just the first page number of the article), the authors of the manuscript are virtually required to check the original article, and this checking increases the likelihood that the entire reference is recorded accurately. Supplying all authors' names allows better identification of the investigators because the last author is more often better recognized than the first author, and by having all authors listed the editor is assisted in the selection of possible manuscript reviewers. (The last author is more likely to be a member of the journal's editorial board than is the first author.) The subtitle might provide more information regarding the actual substance of a publication than the primary title. Listing inclusive page numbers prevents the confusion of a reference to a previously published manuscript with a reference to an abstract, which is never more than 1 page. To diminish the space occupied by references without diminishing their accuracy or usefulness, the type size utilized for printing references in the AJC was significantly reduced beginning in the October 1982 issue.

In summary, references are a reflection of a manuscript's quality and should be selected carefully and recorded accurately.

William C. Roberts, MD
Editor-in-Chief



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CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

[1]Data on file: Key Pharmaceuticals, Inc. 01/83

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NOSOCOMIAL INFECTIONS

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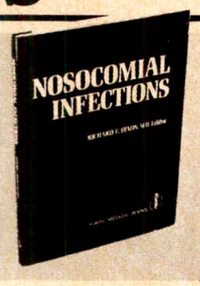

Based on the proceedings of the 2nd International Conference on Nosocomial Infections held August 5 - 8, 1980 in Atlanta, Georgia and sponsored by the Center for Disease Control, this book provides between two covers the most comprehensive, in-depth study of this international problem published in 10 years. This major reference is divided into 11 sections consisting of 50 chapters written by over 100 internationally known experts.

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- An update of disease trends since the 1st International Conference held a decade earlier
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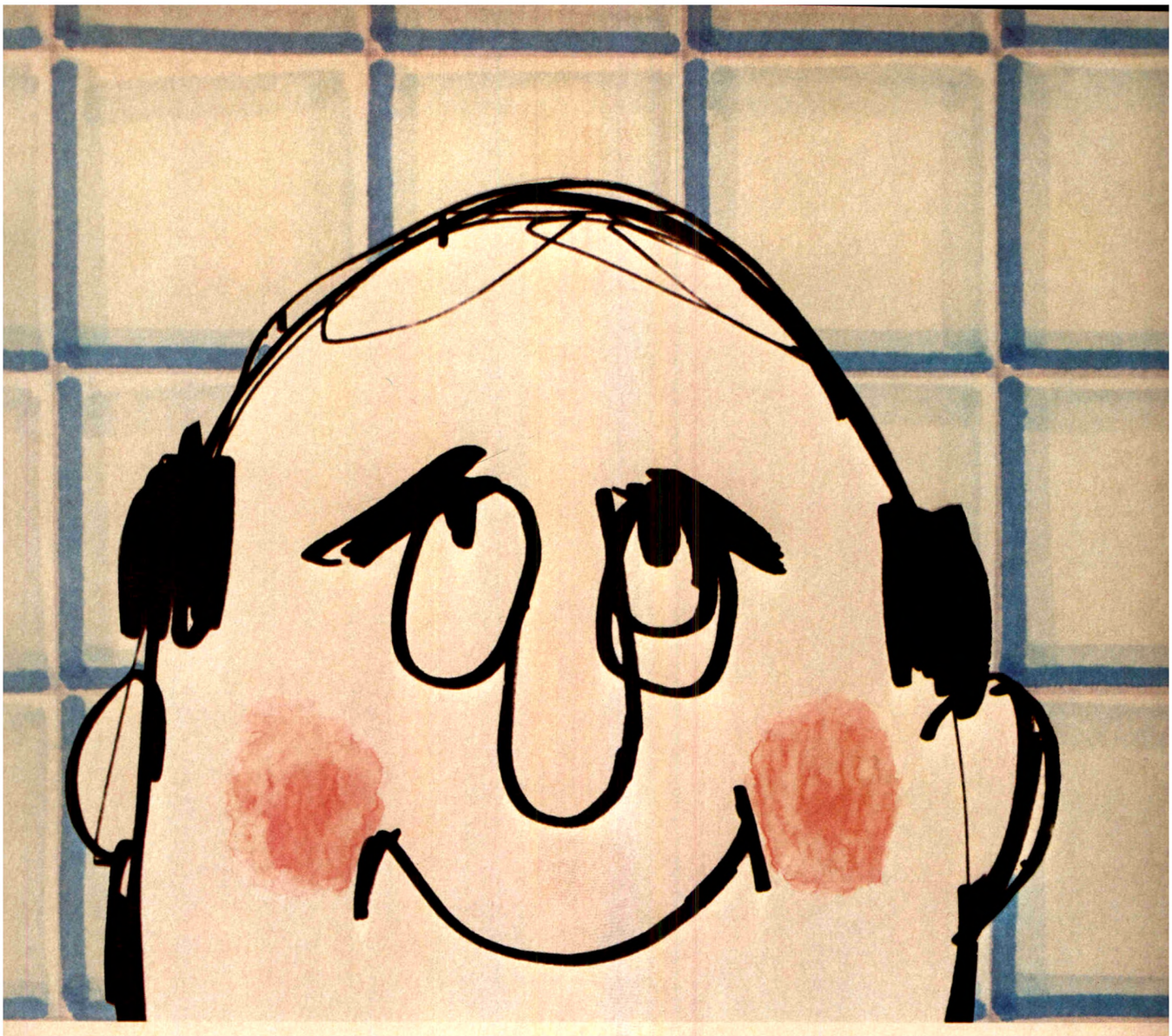

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Modes	DDD, DVI, DAD, VDD, VAT, VVI, DOO, VOO		
Programmed pacing rate, ppm	30 to 120 in 5-ppm increments		
Sensitivity mV (each channel)	Off, 0.5, 1.3, 2.5		
Pulse duration/ output current, ms/mA (each channel)	0.2/2 0.3/3 0.4/4	0.5/5 0.6/6 0.8/8	1.0/10 2.0/12
A-V delay, ms	75, 100, 125, 150, 175, 200, 250		
Refractory, ms (each channel)	250, 300, 350, 400, 500		
Output voltage, V (open circuit)	8 mA or higher below 8 mA	8.4 4.0	
Pace limit, ppm	160		
Battery test rates, magnet applied, ppm	70 62½ 52½	Battery satisfactory Battery nearing depletion Backup pacing (VOO) activated	
Pacing configuration	Unipolar		
Parameters revealed through telemetry	Mode, rate, sensitivity, output current, pulse duration, refractory period, and last two digits of pacer serial number.		

Specifications

Power source	Two Cordis lithium cells
Specific gravity	1.8
Weight, g	73
Thickness, mm	15
Width, mm	57
Height, mm	69
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Important Information—Sequicor II

Indications and Contraindications
The medical literature describes currently accepted indications and contraindications for various pacing/sensing modes. The physician's clinical experience and judgment must ultimately be the guide in selecting the pacing mode best suited to the patient's needs.

Pacing of the ventricles (VVI) is indicated for control of heart rate in patients with A-V block or sick sinus syndrome. *Asynchronous pacing may be contraindicated for long-term pacing when inherent activity is present or is likely to be present in the chamber being paced.* There are no other known contraindications for ventricular pacing to control heart rate.

Atrial-synchronized ventricular pacing (VVD) is indicated for permanent or intermittent complete heart block with normal atrial rhythm. A-V sequential (DVI) pacing is indicated for permanent sinus bradycardia with or without heart block. Automatic dual-chamber demand pacing (DDD) is indicated when there is an A-V conduction disturbance and/or sinus node dysfunction (sinus bradycardia with A-V block or bradytachy syndrome). These atrial pacing modes are intended for patients who would benefit from the restoration of atrial contribution to cardiac output.

Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated for use in the presence of persistent atrial flutter or atrial fibrillation.

Precautions
Use Only Models 255A and 256A Cordis Programmers
Only a Cordis Model 255A Programmer III or Cordis Model 256A Interactive Programmer can be used with the Cordis Model 233F Sequicor pacer. The Sequicor II pacer *will not respond* to programming transmissions from other programmers. Do not use Cordis Models 166 and 222 Omnicor Programmers or programmers of other manufacturers.

"Use Before" Date
To assure maximum service life, pacers must be implanted before the "Use before" date shown on the package label.

Warnings
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Lead—unsatisfactory electrode position, fracture, displacement, perforation of heart wall, faulty connection with pacer, migration through body tissue.

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MAY 1, 1983

The American Journal of CARDIOLOGY®

VOLUME 51

NUMBER 8

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CORONARY HEART DISEASE

1243 Effects of Discontinuing Maintenance Digoxin Therapy in Patients With Ischemic Heart Disease and Congestive Heart Failure in Sinus Rhythm

MIHAI GHEORGHIADE and GEORGE A. BELLER

Twenty-four patients in sinus rhythm with ischemic heart disease and documented congestive heart failure were studied prospectively on and off maintenance oral digoxin therapy. Of these, 88% were receiving concurrent diuretics or vasodilators, or both. At 1 month off digoxin, no difference was observed in the group as a whole in heart failure score, body weight, cardiothoracic ratio, radionuclide left ventricular ejection fraction, or duration of symptom-limited treadmill exercise compared with evaluation on digoxin. By 1 month of digoxin withdrawal, the heart failure score (maximum 12 points) increased by only 1 point in 2 patients. In this study population, cessation of digoxin therapy had no adverse effects.

1251 Efficacy and Safety of Verapamil in Patients With Angina Pectoris After 1 Year of Continuous, High-Dose Therapy

DONALD A. WEINER, CAROLYN H. McCABE, SALLY S. CUTLER, MARK A. CREAGER, THOMAS J. RYAN, and MICHAEL D. KLEIN

The long-term efficacy and safety of high-dose verapamil therapy (480 mg/day) was assessed in 26 patients with chronic stable angina pectoris during a 3-phase protocol: Phase 1—an initial, 6-week placebo-controlled, double-blind crossover assessment; Phase 2—an open label, 1-year follow-up; and Phase 3—a final drug withdrawal and rechallenge 10-week study. Adverse effects during Phase 2 were mild, consisting of constipation (6 patients) and prolongation of the P-R interval (5 patients); however, no patient required alteration of the 480 mg/day dose. The clinical and exercise responses to verapamil compared with placebo were similar during the Phase 3 protocol and during the initial Phase 1 study. These investigations demonstrate that verapamil is safe and effective when evaluated after 1 year of continuous therapy in patients with chronic stable angina using a dose of 480 mg/day.

1256 Enhanced Detection of Proximal Right Coronary Artery Stenosis With the Additional Analysis of Right Ventricular Thallium-201 Uptake in Stress Scintigrams

JACK GUTMAN, MICHAEL BRACHMAN, ALAN ROZANSKI, JAMSHID MADDAHI, ALAN WAXMAN, and DANIEL S. BERMAN

The authors analyzed the accuracy of stress-induced right ventricular thallium defects for detecting proximal right coronary artery stenosis in 35 patients with and 39 without proximal right coronary artery stenosis. The sensitivity and specificity were 59 and 88%, respectively, compared with 67 and 68%, respectively, for left ventricular inferior wall thallium defects. A defect in either the right or the left ventricular inferior wall had the highest sensitivity, 93%, but a specificity of only 56%. When both ventricles had defects, all 9 patients had proximal right coronary artery stenosis; when both ventricles were normal, 26 of 28 had no proximal right coronary artery stenosis. The accuracy of exercise ventriculographic parameters (right ventricular ejection fraction and left ventricular inferior wall motion) were not significantly different. Thus, analysis of the right ventricle adds additional diagnostic information in the assessment of proximal right coronary artery stenosis.

Continued on page A23

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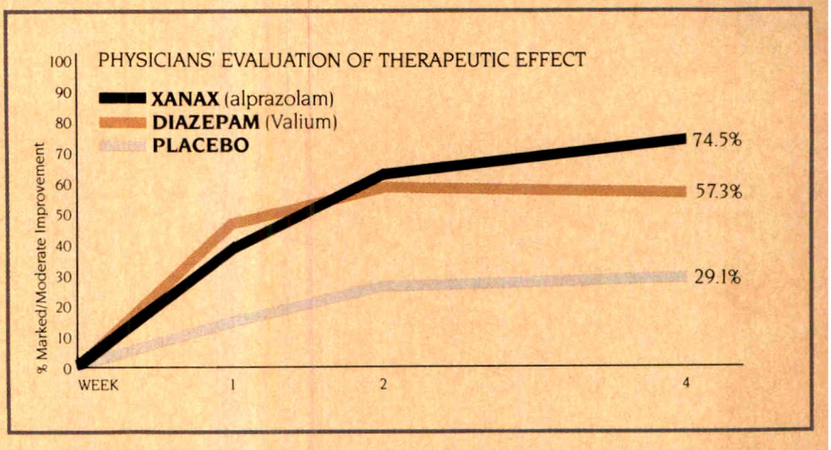

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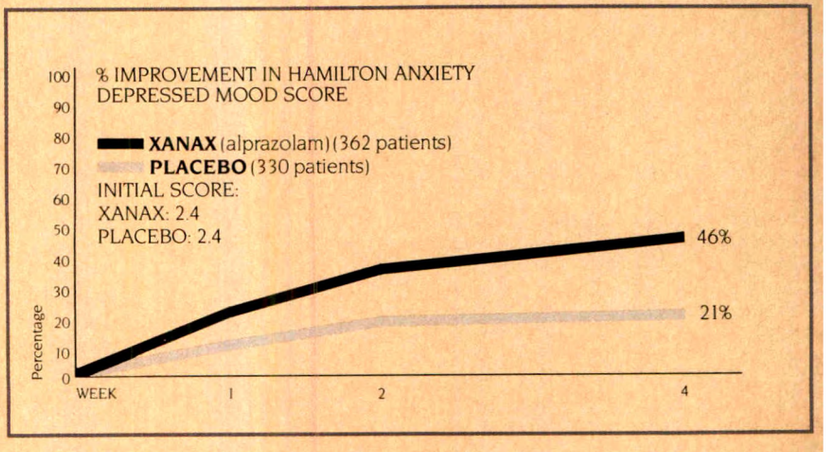

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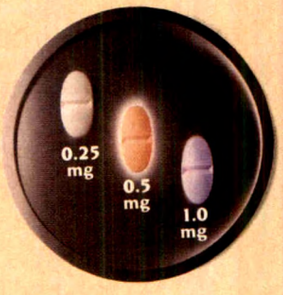

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Please see next page for brief summary of prescribing information.

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CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J *Clin Psychiatry* 42 (9):347-351, 1981.

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CONTENTS

1261 Prognostic and Predictive Value of Exertional Hypotension in Suspected Coronary Heart Disease

K. E. HAMMERMEISTER, TIMOTHY A. DeROUEN, HAROLD T. DODGE, and MAY ZIA

Late survival is impaired in patients whose blood pressure decreases during symptom-limited exercise testing compared with those whose blood pressure increases. However, the continuous variable, maximum systolic pressure during exercise, is a more powerful predictor of survival. Even though patients with exertional hypotension have more extensive coronary artery disease and more severe left ventricular dysfunction than those without, exertional hypotension is an insensitive indicator of left main coronary artery stenosis, 3-vessel disease, or severe resting left ventricular dysfunction.

1267 Effects of a Cardioselective Beta$_1$ Partial Agonist (Corwin) on Left Ventricular Function and Myocardial Metabolism in Patients With Previous Myocardial Infarction

MICHEL F. ROUSSEAU, HUBERT POULEUR, and MARIE-FRANÇOISE VINCENT

Corwin is an orally active beta$_1$ partial agonist, able to stabilize the beta$_1$ adrenoceptors at approximately 43% of their maximal activity. The hemodynamic and metabolic effects of corwin were assessed in 25 patients with a previous myocardial infarction. The data indicate that corwin is a positive inotrope, able to improve the left ventricular systolic and diastolic function without increasing myocardial oxygen consumption.

1275 Relation of Segmental Wall Motion to Global Left Ventricular Function in Acute Myocardial Infarction

FUMITAKA OHSUZU, CHARLES A. BOUCHER, JOHN B. NEWELL, TSUNEHIRO YASUDA, HERMAN K. GOLD, ROBERT C. LEINBACH, KENNETH A. McKUSICK, ROBERT D. OKADA, SIMON ROSENTHAL, GERALD M. POHOST, and H. WILLIAM STRAUSS

The relationship of left ventricular regional wall motion to global ventricular function was evaluated by radionuclide ventriculography in 127 patients within 18 hours of acute myocardial infarction. No patient had evidence of a previous infarction. The following parameters were measured: (1) wall motion index, (2) percent abnormally contracting segment, (3) ejection fraction (EF), (4) end-diastolic (EDV) and end-systolic volume (ESV), and (5) peak systolic cuff pressure/end-systolic volume ratio (PSP/ESV). The measurements of global function correlated well with wall motion index ($r = 0.83$, $p < 0.001$ for EF; $r = -0.69$, $p < 0.001$ for ESV; and $r = 0.61$, $p < 0.001$ for PSP/ESV), but EDV correlated less well ($r = -0.35$, $p < 0.001$). Multiple linear regression analysis revealed that EF correlated best with wall motion index, and no other parameter of global left ventricular function added significantly to the regression.

1282 Effect of Metoprolol on Indirect Signs of the Size and Severity of Acute Myocardial Infarction

JOHAN HERLITZ, DAG ELMFELDT, ÅKE HJALMARSON, STIG HOLMBERG, IVAN MÁLEK, GUNNAR NYBERG, LARS RYDÉN, KARL SWEDBERG, ANDERS VEDIN, FINN WAAGSTEIN, ANDERS WALDENSTRÖM, JOHAN WALDENSTRÖM, HANS WEDEL, LARS WILHELMSEN, and CLAES WILHELMSSON

In a double-blind randomized trial including 1,395 patients with suspected acute myocardial infarction (MI), the effect of the beta$_1$-selective adrenoceptor antagonist metoprolol on indirect signs of the size and severity of the infarction was evaluated. Metoprolol (15 mg) was given intravenously and followed by oral administration for 3 months (200 mg daily). Placebo was given in the same way. A lower serum enzyme activity (heat stable lactate dehydrogenase [LD] and less Q- and R-wave changes in the electrocardiogram (precordial mapping) were found in patients treated with metoprolol ≤ 12 hours after the onset of pain, whereas no difference was found in patients treated later. Patients treated with metoprolol ≤ 12 hours also showed a decreased need for furosemide, shorter duration of hospitalization, and improved 1-year survival compared with placebo, whereas no difference was found in those treated later.

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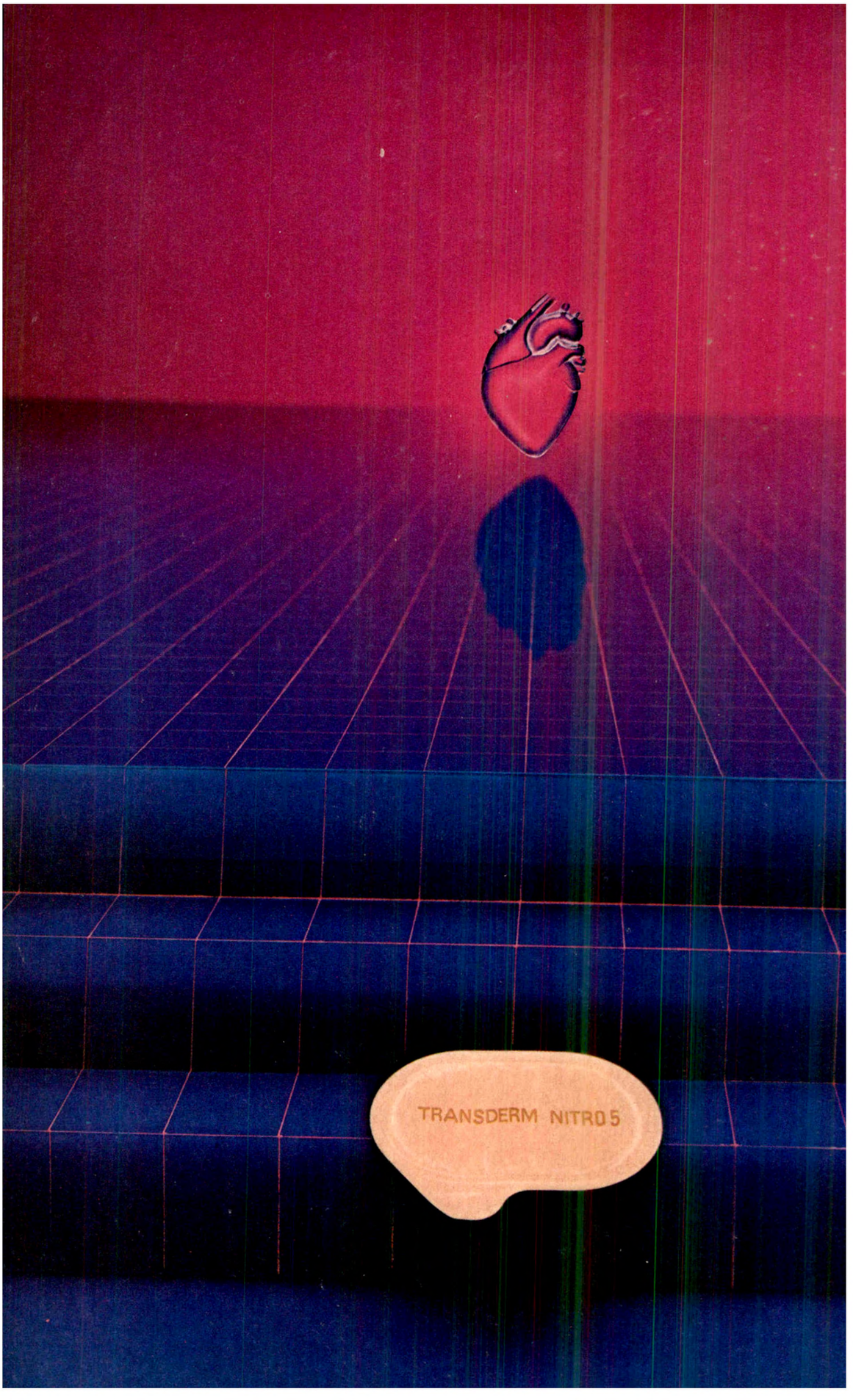
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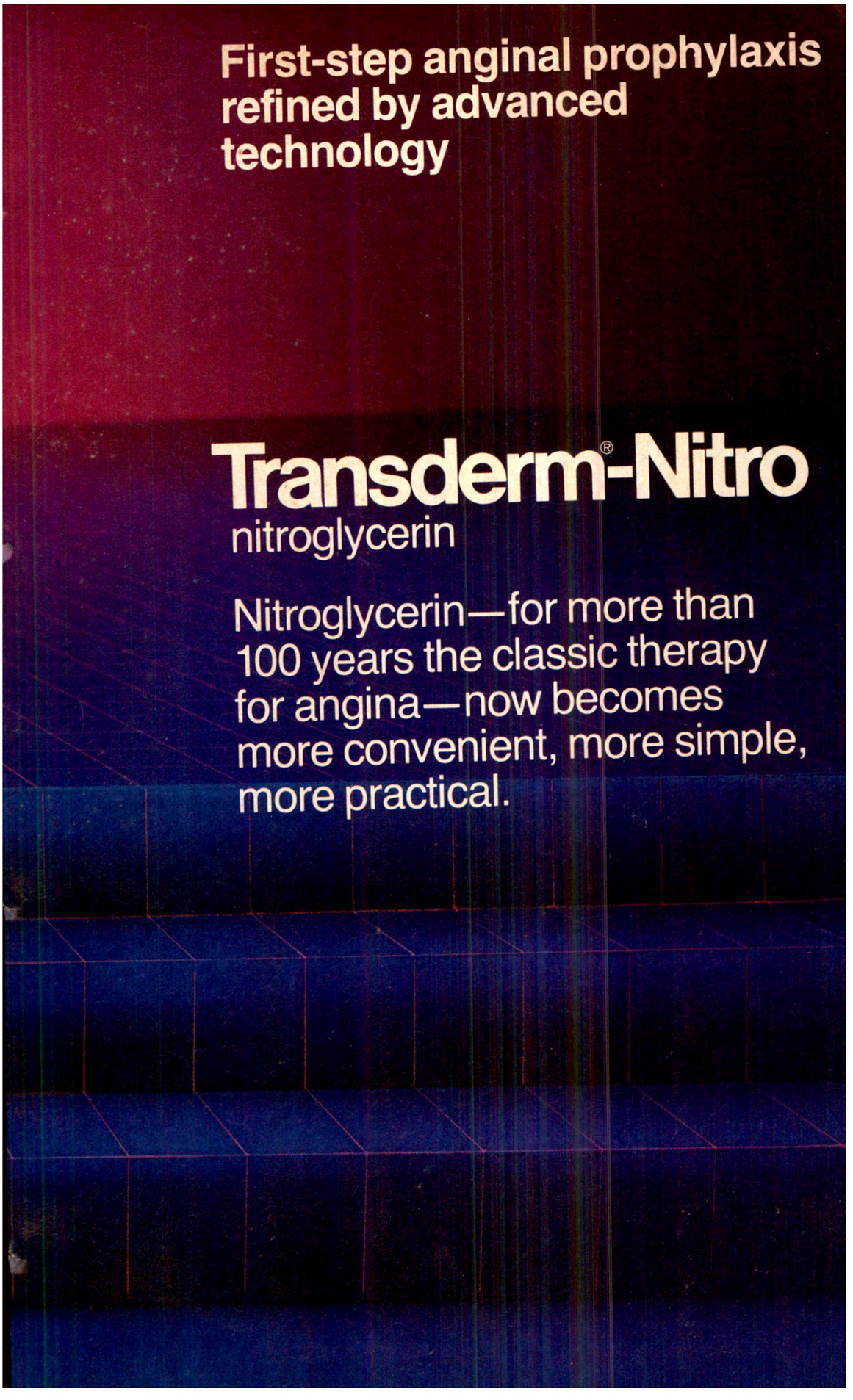
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Small, cosmetically acceptable and well tolerated.
Will not leak or stain clothing. May even be worn while bathing or swimming. Few reports of skin irritation.

Note: Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

*Black CD: Transdermal drug delivery systems. *US Pharmacist* 1982 (Nov); 7(11):49-78.

Before prescribing, please read full Prescribing Information.

C I B A

Transderm®-Nitro

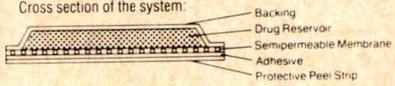
(nitroglycerin)
Transdermal Therapeutic System

DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semi-permeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system: 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

Dist. by:
CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

C82-16 (3/82)

CONTENTS

1289 Role of Myocardial Ischemia in the Genesis of Stress-Induced S-T Segment Elevation in Previous Anterior Myocardial Infarction

HENRY GEWIRTZ, MICHAEL SULLIVAN, GEORGE O'REILLY, STEVEN WINTER, and ALBERT A. MOST

This study tests the hypothesis that myocardial ischemia is responsible for exercise-induced S-T segment elevation in patients with previous anterior myocardial infarction (MI). To accomplish this goal, exercise stress testing in conjunction with thallium imaging of the myocardium was performed in 28 such patients. Two groups of patients were identified: Group I exhibited new or increased S-T segment elevation in precordial leads V_1 to V_6 in response to stress, while Group II did not. Evidence of abnormal thallium washout from myocardial scan segments (that is, imaging evidence of ischemia) occurred in 12 of 15 Group I patients versus 9 of 13 in Group II (difference not significant). Group I patients, however, had larger anterolateral plus septal initial thallium uptake defects than did Group II patients. Similarly, resting left ventricular ejection fraction was lower in Group I than in Group II. Multiple stepwise linear regression analysis demonstrated that the extent of S-T elevation induced by stress correlated best with the size of the initial anterolateral plus septal thallium uptake defect score and to a lesser extent with resting ejection fraction and change in heart rate from rest to peak stress (corrected correlation coefficient = 0.76, $p < 0.001$). Thus, in patients with previous anterior MI, myocardial ischemia is not required for production of stress-induced S-T segment elevation. The latter likely reflects the extent of previous anterior wall damage and to a lesser extent the increase in heart rate between rest and peak stress.

1294 Enzymatic Estimation of Myocardial Infarct Size When Early Creatine Kinase Values Are Not Available

JANET L. SMITH, DIETER AMBOS, HERMAN K. GOLD, JAMES E. MULLER, W. KENNETH POOLE, DANIEL S. RAABE, Jr., ROBERT E. RUDE, EUGENE PASSAMANI, EUGENE BRAUNWALD, BURTON E. SOBEL, ROBERT ROBERTS, and the MILIS Study Group

Estimates of myocardial infarct (MI) size from plasma creatine kinase (CK) in patients admitted after the initial elevation in CK may be considerably smaller than estimates based on the total plasma CK curve. Estimates of MI size based on data inclusion intervals beginning a 24, 12, 8, and 4 hours before peak CK were 11, 14, 23, and 47% less than values based on complete CK curves. We prospectively derived correction factors from a population of 120 patients with complete, total, and MBCK time activity curves. These correction factors were then applied to a new population (n = 25) with complete CK curves to compensate for purposely omitted early CK values. The corrected estimates of MI size were within 7% of those based on the complete CK curves. Thus, if peak plasma CK is known, underestimation of MI size can be compensated for despite the unavailability of early CK values. Since 90% of patients present to the hospital before plasma CK activity has reached maximum values, MI size can be estimated in nearly all patients and is thus a more widely applicable endpoint for use in clinical trials and patient management.

1301 Series Exercise Testing Up to 6 Years After Coronary Bypass Surgery: Behavior of Exercise Parameters in Groups With Different Degrees of Revascularization Determined by Postoperative Angiography

HELMUT GOHLKE, CHRISTA GOHLKE-BÄRWOLF, LADISLAUS SAMEK, PETER STÜRZENOFECKER, MARTIN SCHMUZIGER, and HELMUT ROSKAMM

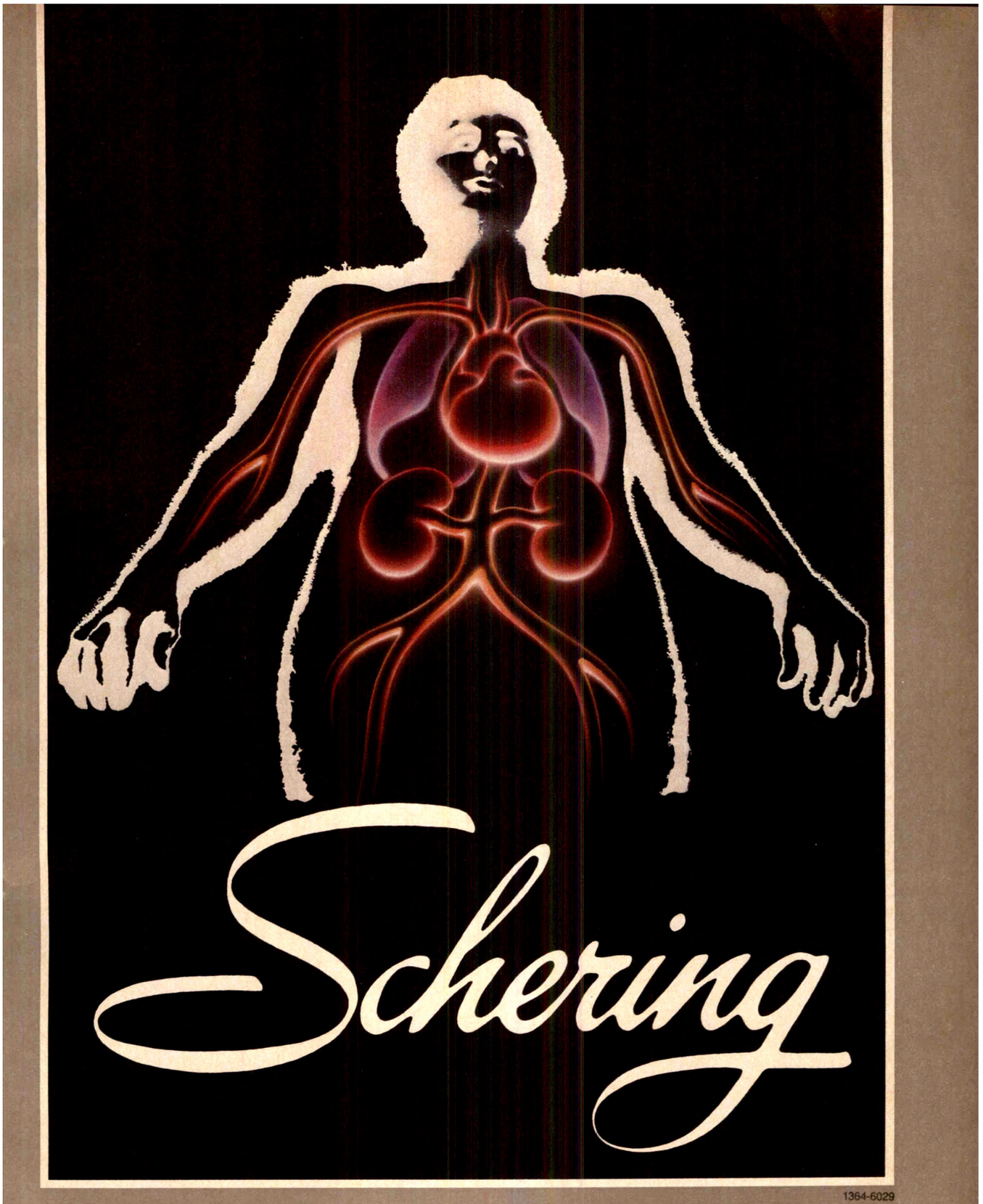
Four hundred thirty-five patients who had undergone angiography after coronary artery bypass grafting (CABG) were followed by serial exercise testing up to 6 years after CABG. One hundred eighty-two, 176, and 54 patients were completely, sufficiently, or incompletely revascularized, respectively, and 20 patients had all grafts occluded. Patients with complete revascularization showed improvement of all exercise parameters lasting for 6 years, patients with sufficient revascularization for 4 years, and patients with incomplete revascularization for 1 year only. Patients with all grafts occluded showed improvement of only some exercise parameters. The completeness of revascularization determines the extent and duration of improvement of exercise parameters.

1307 Cardiokymography During Exercise Testing: A New Device For the Detection of Coronary Artery Disease and Left Ventricular Wall Motion Abnormalities

DONALD A. WEINER, CAROLYN H. McCABE, GINA DAGOSTINO, SALLY S. CUTLER, and THOMAS J. RYAN

The cardiokymograph is a device that has been shown to reflect left ventricular wall motion abnormalities. Its accuracy in detecting coronary artery disease during treadmill exercise testing was assessed in 204 consecutive patients undergoing coronary arteriography. The sensitivity and specificity were similar for both the exercise

Continued on page A32

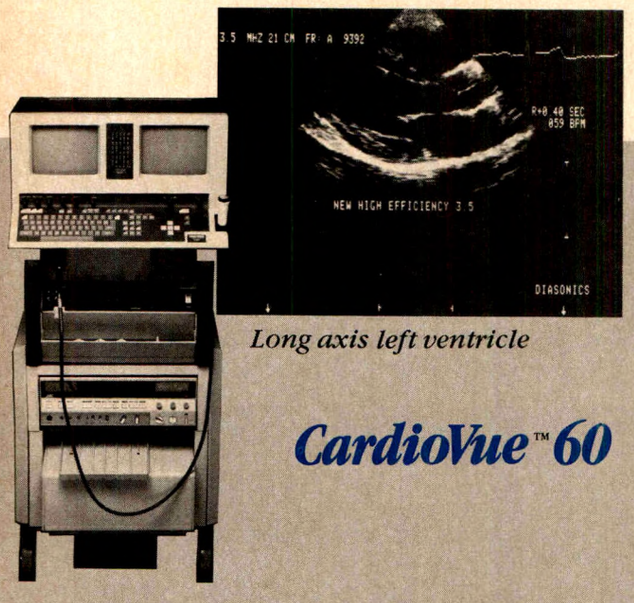


1364-6029

A familiar name in medicine becomes a new name in cardiovascular therapy.

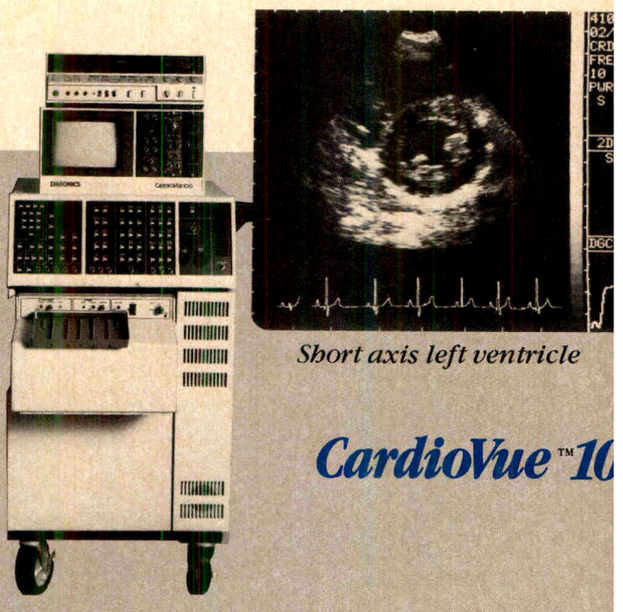
DIASONICS

CARDIAC IMAGING.....



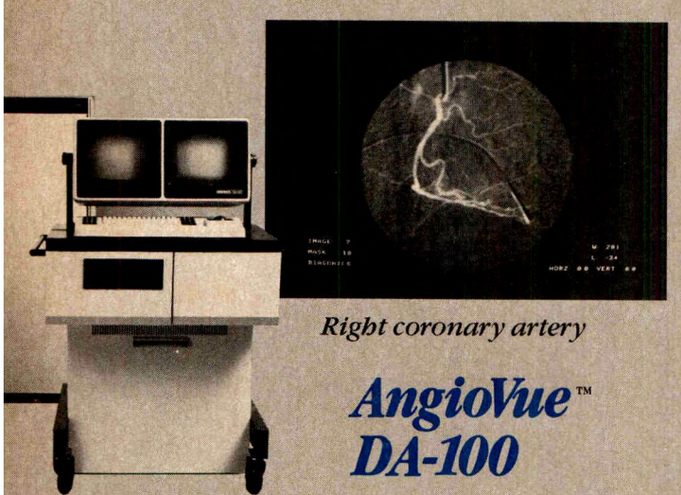
Long axis left ventricle

CardioVue™ 60



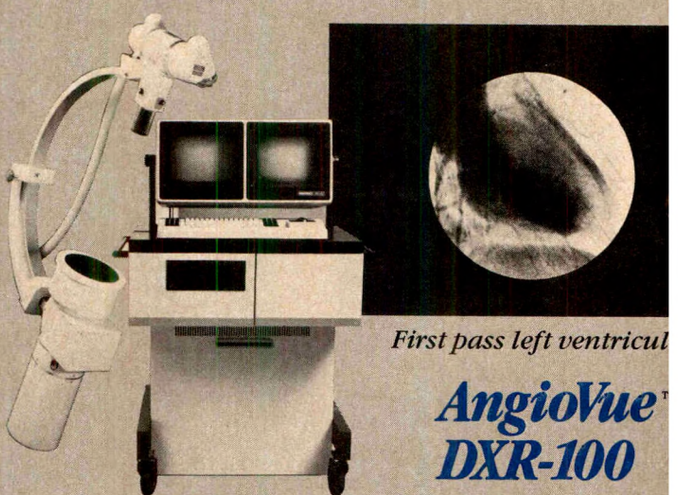
Short axis left ventricle

CardioVue™ 10



Right coronary artery

AngioVue™ DA-100

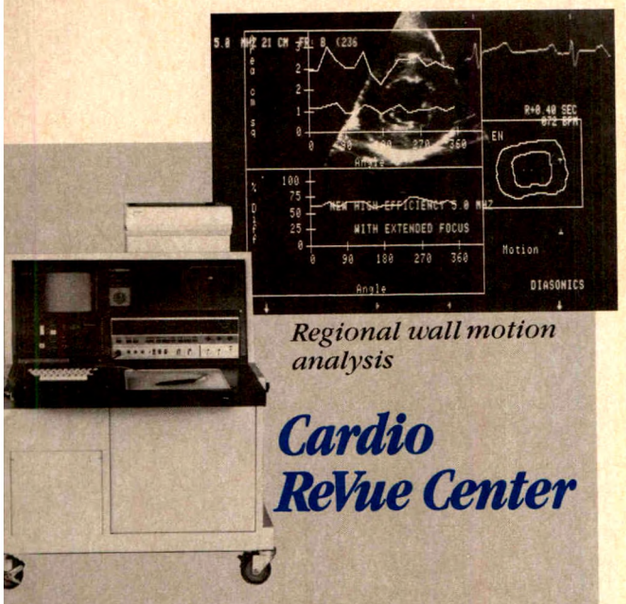


First pass left ventricul

AngioVue™ DXR-100

IT'S WHERE IMAGING IS GOING..

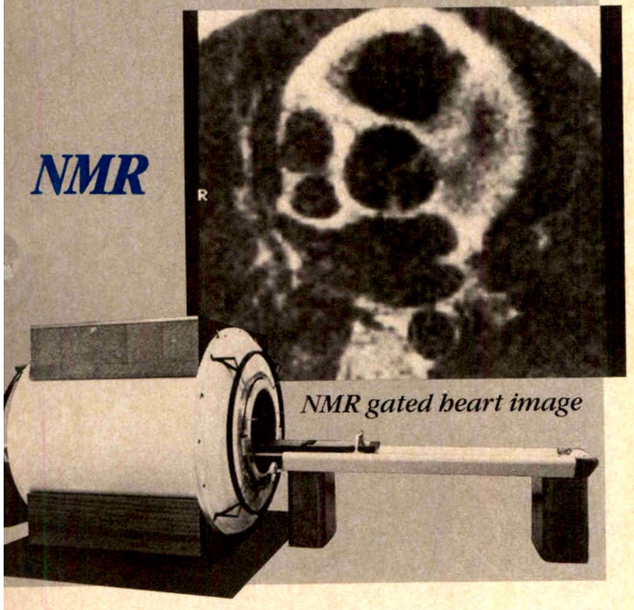
TODAY AND TOMORROW



Regional wall motion analysis

Cardio ReVue Center

NMR



NMR gated heart image

DIASONICS

DIASONICS, INC.
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CardioVue™ 60 NewImage™ Phased Array

Diasonics' CV-60 is small, portable and ideal for a wide range of cardiac imaging applications.

It produces excellent, high quality images with a new, compact, wide-aperture transducer. System features include: ■ Outstanding image quality, clinical versatility and portability ■ Upgradable computer-based design ■ 50% improvement in lateral resolution ■ Multigate Doppler system capabilities.

CardioVue™ 100 Mechanical Sector Scanner

Diasonics' CV-100 is the smallest full function cardiac mechanica sector scanner available, with a proven history of upgradability and software enhancements. System features include: ■ Digital RF Ultrasound™ for superior resolution and enhanced low level echoes ■ MicroSector™ probes — smallest 16mm crystal design available ■ Pulsed and CW Doppler capabilities ■ Wide range of probes for every application.

Cardio ReVue Center

Diasonics' Cardio ReVue Center meets quantitative diagnostic requirements with: ■ Calculation/display of cardiac parameters ■ Graphics/printing/patient reports ■ User programmability ■ Digital data acquisition.

AngioVue™ DA-100

Diasonics' DA-100 produces digital images clinically equivalent to cine film, with added image manipulation and enhancement capabilities. The DA-100 provides the cath lab with advanced digi subtraction imaging and all the benefits of computerized analys ■ Totally digital coronary artery imaging ■ Quantitative ventri ulography ■ High frame rate processing/image enhancement.

AngioVue™ DXR-100

Diasonics' DXR-100 is the first standalone system for intravenous ventriculography. By combining the Diasonics/OEC 9-inch C-Arm with the Diasonics digital processor, the DXR-100 perform digital subtraction studies in or out of the cath lab. System featu include: ■ Boosted fluoro for better resolution ■ Continuous imaging at 30 fps ■ Total microprocessor system control ■ Cardiac analysis software package.

NMR Imaging

The Diasonics NMR Imaging System can simultaneously image 15 sections in 6.5 minutes with high spatial resolution and excel soft tissue contrast. With its gated imaging capability, NMR will play a major role as a diagnostic tool for the cardiovascular syst

Diasonics has filed a Pre-Market Approval application with the Food and Drug Administration. However, until approval of t application has been obtained, the Diasonics NMR Imaging System is a research device for investigational use.

CONTENTS

electrocardiogram (66 and 86%, respectively) and the exercise cardiokymogr
Among 55 patients who had simultaneous exercise radionuclide ventriculograp
tion abnormalities were found in 79% (23 of 29) of patients with abnormal ca
19% (5 of 26) of patients with normal cardiokymographs ($p < 0.001$). It is conc
during exercise testing accurately reflects left ventricular wall motion abnorma
improve the diagnostic accuracy of exercise testing as an additional marker of

**1312 Rest and Redistribution Thallium-201 Myocardial Scintigraphy to Predict In
Ventricular Function After Coronary Arterial Bypass Grafting**

ABDULMASSIH S. ISKANDRIAN, A-HAMID HAKKI, SALLY A. KANE, INDE
ELDRED D. MUNDTH, A-HADI HAKKI, and BERNARD L. SEGAL, *With the*
ANGELO AMENTA

This study examines the value of rest and redistribution thallium-201 imaging t
ventricular ejection fraction after coronary artery bypass grafting (CABG) in 26 p
ease and abnormal left ventricular function. Nineteen patients had pathologic Q
erin intervention radionuclide ventriculograms were obtained in 20 patients bef
that rest and redistribution thallium imaging is useful in identifying patients whose
prove after CABG. Normal rest images or reversible resting defects correctly ide
who showed improvement after CABG. Nitroglycerin intervention ventriculograp
less useful in this differentiation.

SYSTEMIC HYPERTENSION

**1317 Long-Term Converting-Enzyme Inhibition as a Guide to Surgical Curability c
With Renovascular Disease**

JAN STAESSEN, CHRISTOPHER BULPITT, ROBERT FAGARD, PAUL LIJNEN

In 27 hypertensive patients with renovascular disease, average blood pressure l
term converting-enzyme inhibition (CEI) with captopril and after surgery. Systolic
lated with postoperative systolic pressure ($r = +0.53$; $p < 0.01$), while diastolic
together with circulating renin ($p < 0.01$) contributed independently to postoperati
$p < 0.001$). Blood pressure during long-term CEI may therefore be useful as a pr
sure.

**1323 Nifedipine Tablets for Systemic Hypertension: A Study Using Continuous Am
Recording**

ROBERT S. HORNUNG, BRIAN A. GOULD, RODERICK I. JONES, TANSUKH
EDWARD B. RAFTERY

The authors examined the profile of blood pressure (BP) reduction over 24 hour
ment with nifedipine tablets, which have a lower peak plasma level and longer h
sules. Seventeen fully ambulant subjects with essential hypertension were studie
arterial recording techniques. The dosage was adjusted from 20 to 60 mg twice da
surements. The mean treatment period was 12.6 weeks. During each ambulatory r
logic testing, including dynamic and isometric exercise, was undertaken. Nifedipir
significant ($p < 0.001$) BP reduction consistently throughout 24 hours. The circadia
Peak BP in response to dynamic and isometric exercise was also significantly re
unduly troublesome. Nifedipine in tablet form given twice daily was shown to redu
during exercise testing.

1328 Instructions to Authors

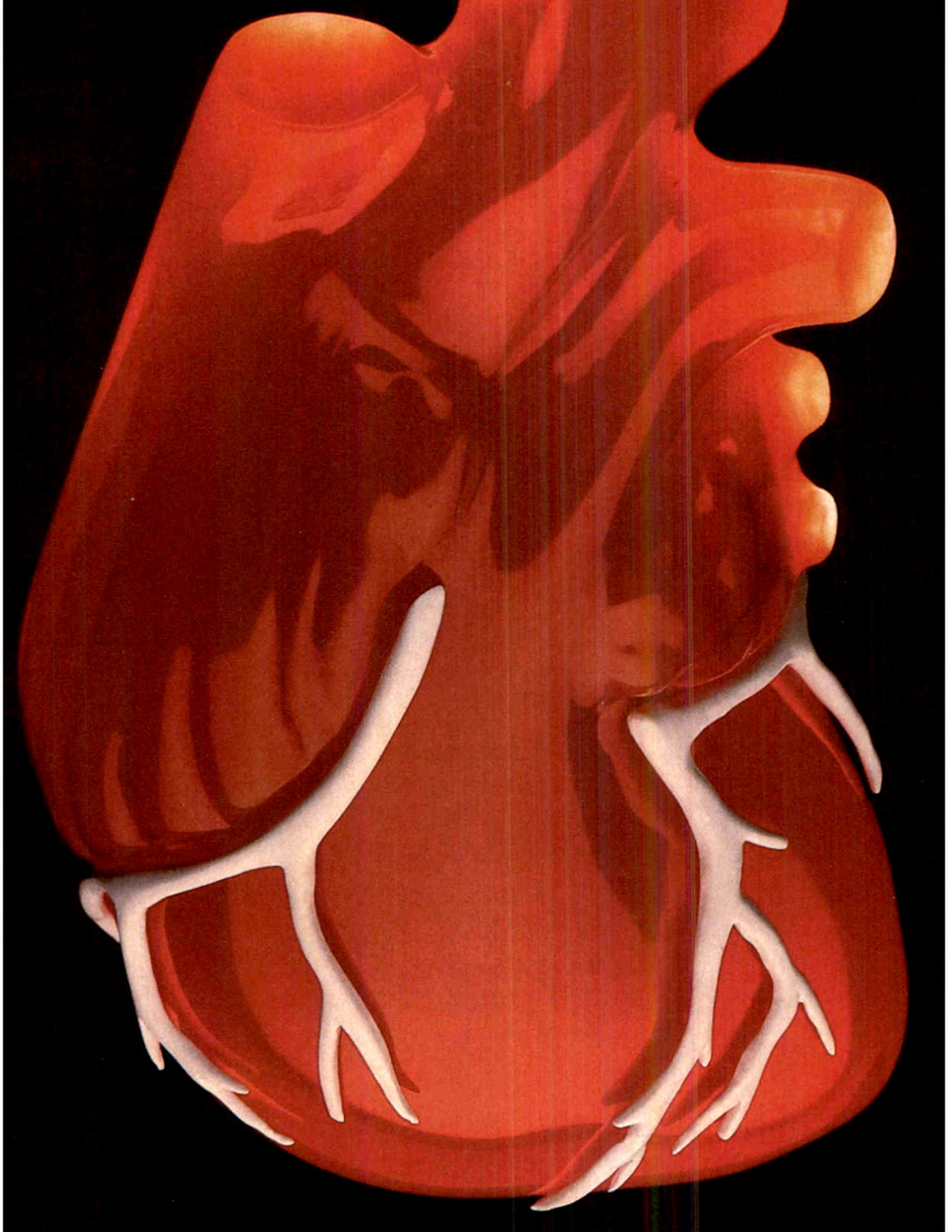
Continued on page A40

in cardiovascular therapy

New CARDIZEM™ (diltiazem HCl)

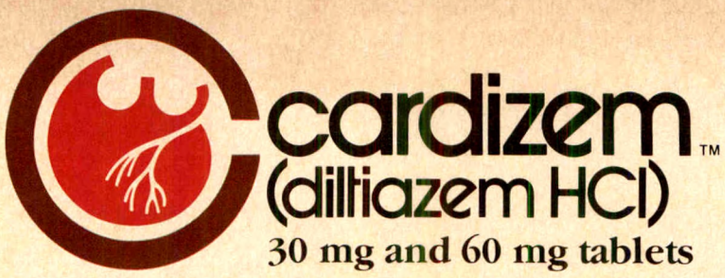
CALCIUM CHANNEL BLOCKADE

from Marion Laboratories



Potent coronary vasodilation with a distinctive hemodynamic profile

Please see full prescribing information on last



INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY WITH A LOW INCIDENCE OF SIDE EFFECTS

CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

These changes provide effective therapy with a low incidence of side effects.

Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

© 1983, Marion Laboratories, Inc.

CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries.[1]

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

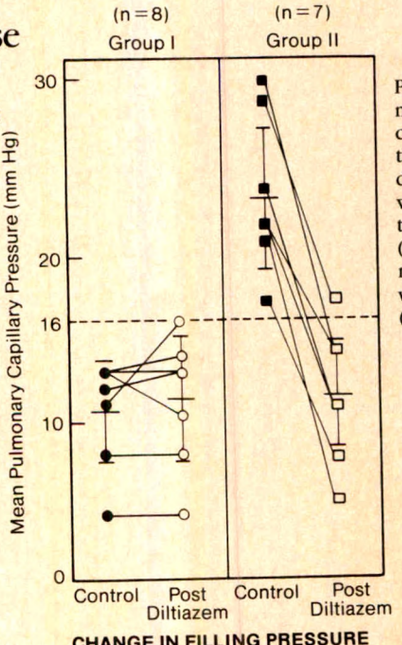
While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.



CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

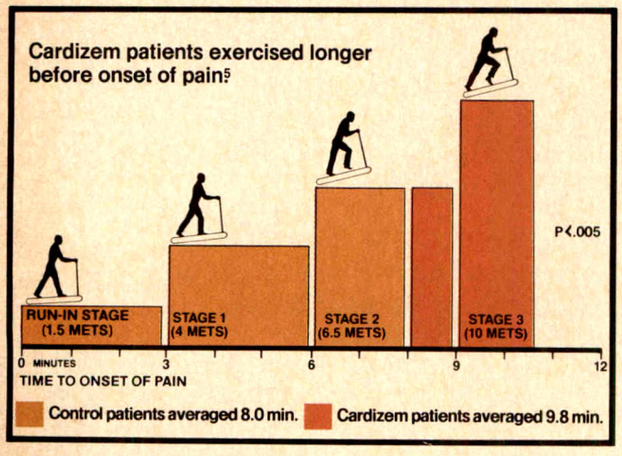
REFERENCES:

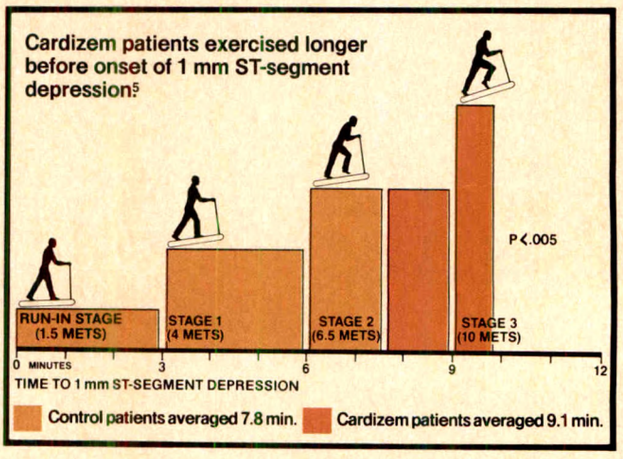
1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.

Please see full prescribing information on last page of this ad.

EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:

A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

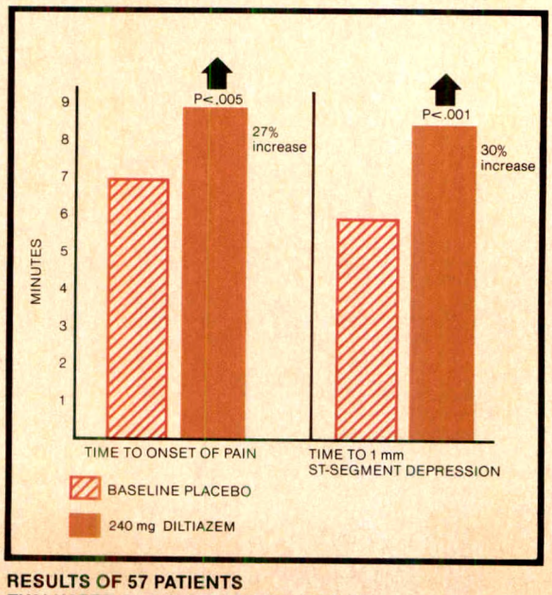
5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.

6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

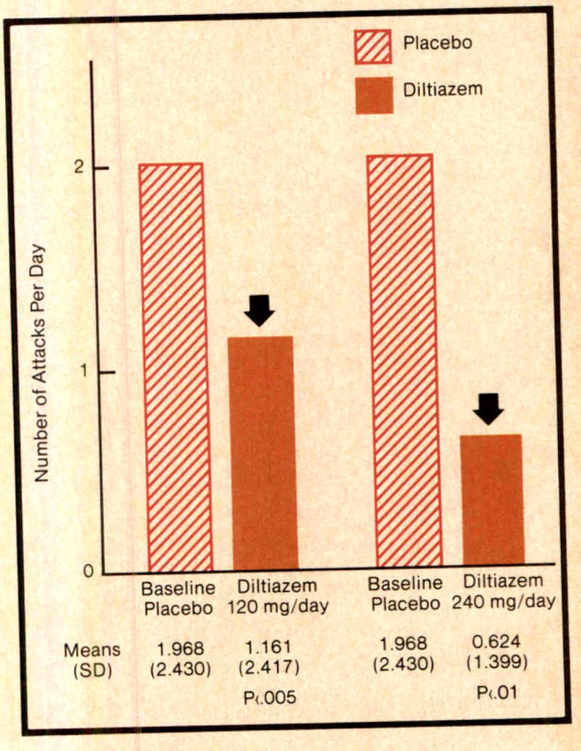
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



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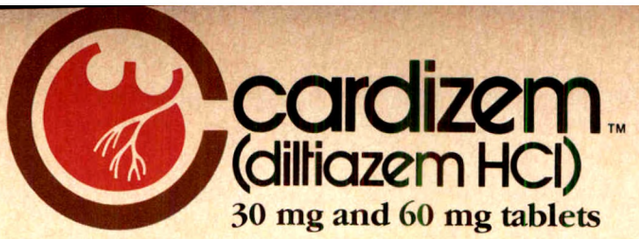
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

Please see full prescribing information on last page of this ad.



LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

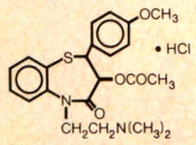
In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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1/83

CONTENTS

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1329 Relation Between Site of Origin of Ventricular Tachycardia and Relative Left Ventricular Myocardial Perfusion and Wall Motion

THOMAS M. McFARLAND, DAVID M. McCARTHY, P. TODD MAKLER, Jr., and MARK E. JOSEPHSON

Eighteen patients with a history of recurrent sustained ventricular tachycardia underwent thallium-201 myocardial perfusion imaging and resting radionuclide ventriculography, and the results were correlated with the tachycardia site of origin (determined by endocardial mapping). All 18 patients had coronary artery disease, and 16 had left ventricular aneurysm. In most patients, the tachycardia site of origin was the periphery of a resting thallium-201 defect and the border of the aneurysm. These results help to explain the pathophysiologic aspects of this arrhythmia and provide noninvasive support for the current surgical approach in patients refractory to medical management.

1334 Ultrarapid Single-Capture Train Stimulation for Termination of Ventricular Tachycardia

JOHN D. FISHER, ELIOT OSTROW, SOO GYUM KIM, and JEFFREY A. MATOS

Some well-tolerated ventricular tachycardias can be terminated by critically timed premature pacer stimuli. Studies of such tachycardias have indicated that the termination zone for single extrastimuli begins immediately after the effective refractory period. Ultrarapid train stimulation, at 50 to 100 Hz (3,000 to 6,000 beats/min) of a duration limited to achieve only a single capture, provides the most efficient method of assuring stimulation during the termination zone. In this study single ventricular extrastimuli and ultrarapid trains were compared in 21 patients with well-tolerated ventricular tachycardia.

CONGESTIVE HEART FAILURE

1339 Hemodynamic and Myocardial Performance Characteristics After Verapamil Use in Congestive Heart Failure

JACK FERLINZ and P. DENNIS CITRON

Administration of the calcium-channel blocking agent verapamil is thought to be contraindicated in the presence of congestive heart failure (CHF) because of the drug's intrinsic negative inotropic effect. Yet, as CHF is frequently associated with arrhythmias and angina pectoris, and verapamil possesses potent antiarrhythmic and antianginal properties which could be of great benefit to selected patients with CHF, this study was undertaken to determine whether verapamil can be given to such subjects with relative safety. For this purpose, 14 patients with CHF were studied with a combined hemodynamic-cineangiographic approach before and after intravenous verapamil administration. Verapamil markedly lowered mean aortic pressure and systemic vascular resistance. Simultaneously, indexes of left ventricular performance substantially improved: ejection fraction increased from 29 ± 13 to 37 ± 17% ($p < 0.01$), and mean velocity of circumferential fiber shortening increased from 0.45 ± 0.18 to 0.64 ± 0.28 circ/s ($p < 0.001$). Therefore, the intrinsic negative inotropic activity of intravenous verapamil in therapeutic doses generally does not represent a serious drawback even in patients with CHF because its potent unloading vasodilatory properties more than compensate for any intrinsic decrease in left ventricular contractility, and can thereby actually improve overall cardiac function.

1346 Efficacy of Prazosin in the Management of Chronic Congestive Heart Failure: A 6-Month Randomized, Double-Blind, Placebo-Controlled Study

ROY V. MARKHAM, JAMES R. CORBETT, ALYCE GILMORE, WILLIAM A. PETTINGER, and BRIAN G. FIRTH

The effect of prazosin, 20 mg/day, on hemodynamic function at rest and on peak upright bicycle exercise (by radionuclide ventriculography), plasma renin activity, catecholamine levels, exercise time and work load, and standard clinical variables were assessed in 23 patients with stable class III symptoms of congestive heart failure. The study comprised a 6-month randomized, double-blind, controlled evaluation of prazosin and placebo in patients on a stable dose of digitalis and diuretics for at least 1 month. Compared with placebo, prazosin caused no demonstrable effect on symptoms of congestive heart failure, exercise time or work load, radionuclide variables, plasma renin activity, or catecholamine levels at any time. Thus, chronic prazosin therapy produced no subjective or objective improvement compared with placebo in the patients with congestive heart failure who were studied.

Continued on page A45

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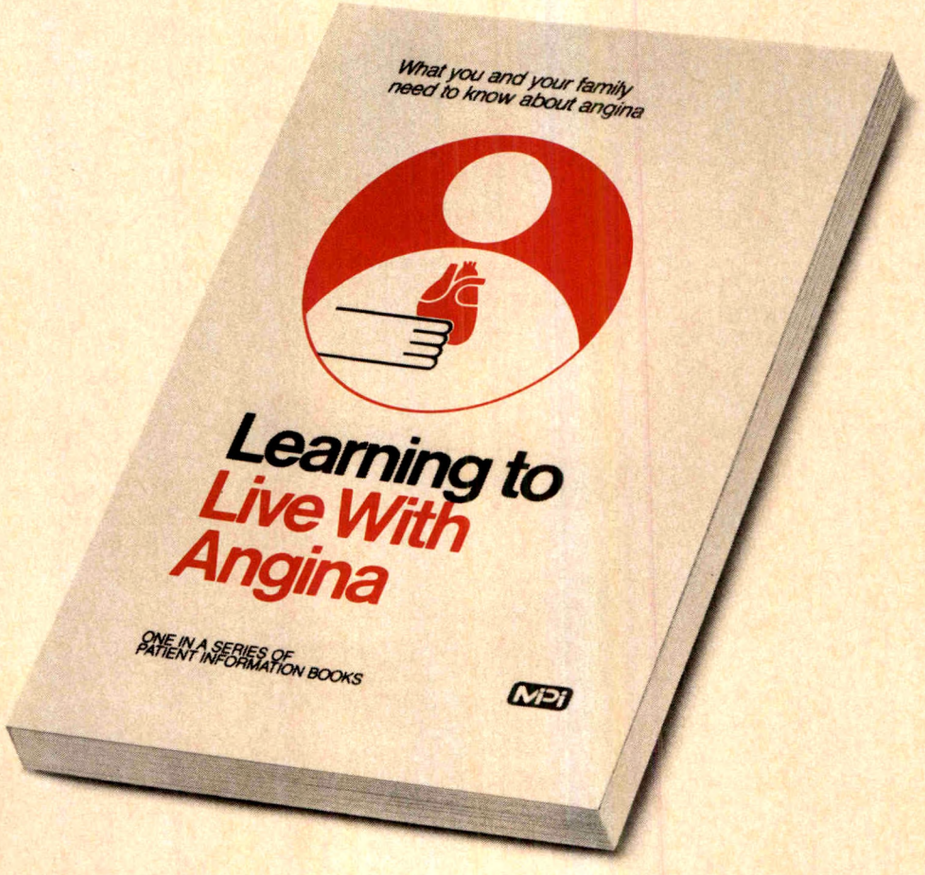

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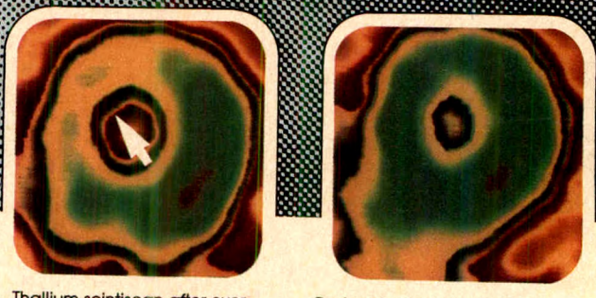
PRIORITIES IN TREATMENT OF ANXIOUS



Thallium scintiscan after exercise, showing marked anterior wall perfusion defect (arrow) before angioplasty.[1]

Postangioplasty thallium scintiscan showing no perfusion defect after peak exercise.[1]

FIRST THE BENEFITS OF PRIMARY MEASURES

Never before have physicians had so many resources for dealing effectively with cardiac disease. Now numerous cardiovascular medications are available—antianginal preparations, antihypertensives, diuretics, calcium antagonists, digitalis, quinidine, vasodilators. Besides these many agents, there are proven surgical procedures such as coronary bypass and valve replacement—and nonsurgical procedures such as angioplasty, which is fast becoming an accepted method of treating severe arterial stenoses.[1] The efficacy of angioplasty is illustrated in the above scintiscans. Yet, even with so many primary measures for improving the patient's cardiovascular status, secondary problems may adversely affect convalescence. One such problem may be excessive anxiety.[2]

References: 1. Vawter MH: *Continuing Education* 1(2):17-24, Aug 1982. 2. Wenger NK: *Cardiovasc Reviews & Reports* 2:1249-1260, Dec 1981. 3. Kucharski A: *Am Fam Physician* 17(3):154-157, Mar 1978.

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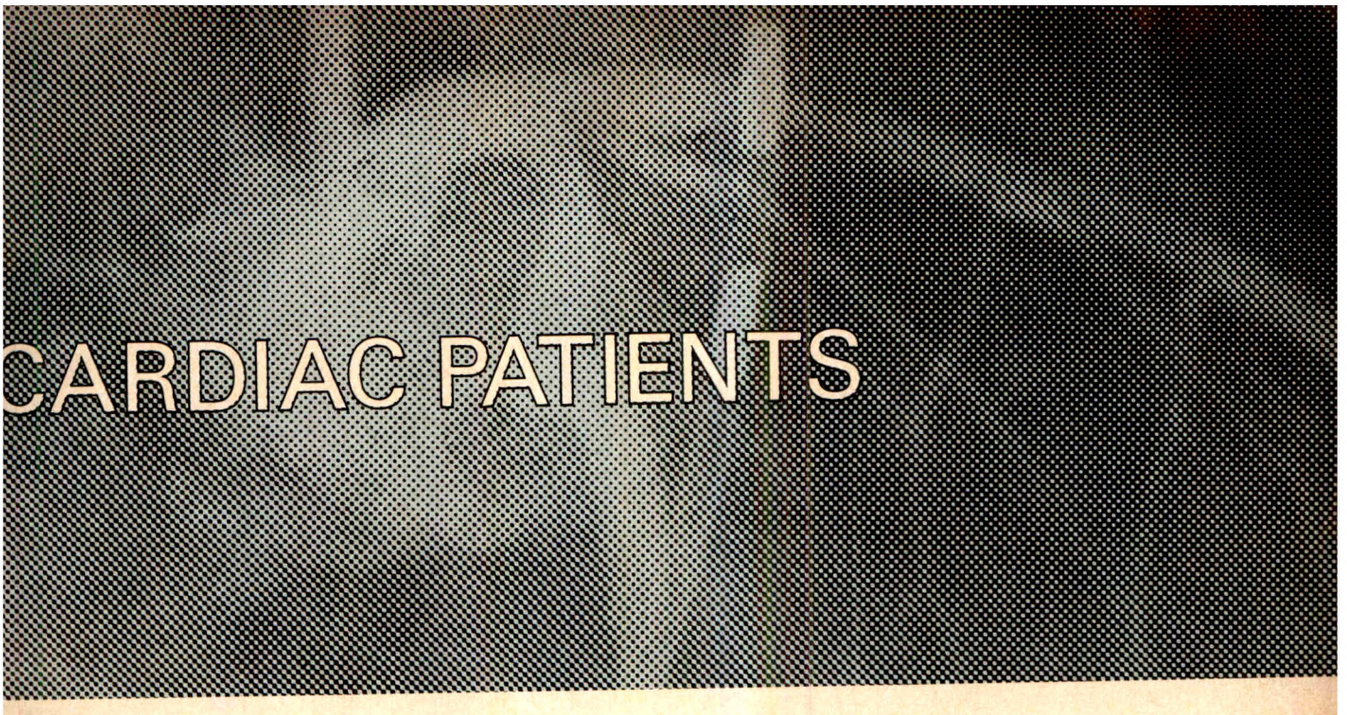

SECOND THE BENEFITS OF ADJUNCTIVE ANTIANXIETY MEASURES

Anxiety in cardiac patients during recovery is a frequent response to symptoms such as chest pain, arrhythmias, breathlessness and weakness.[3] Often, anxiety can be allayed by supportive measures, such as encouraging the patient to express his fears openly, offering reassuring explanations for postcoronary symptoms and, when necessary, prescribing antianxiety medication.[3] For valid reasons, the medication often chosen is Valium® (diazepam/Roche). Its record of efficacy and safety is universally acknowledged. Little or no cardiotoxicity has been reported. Also, Valium is used with most primary cardiac medications. As with all CNS-acting agents, patients should be cautioned against drinking alcohol and against engaging in activities requiring complete mental alertness. Used judiciously, Valium can be a valuable adjunct to rehabilitative measures and can help the cardiac patient employ his own coping devices to good effect.

VALIUM®

diazepam/Roche

2-mg, 5-mg, 10-mg scored tablets

Second to none in pharmacotherapy of anxiety

Please see next page for summary of complete product information.

ROCHE®

VALIUM® (IV)
diazepam/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. or q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500; Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10.

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CONTENTS

1353 Acute Hemodynamic Effects of Endralazine: A New Vasodilator for Chronic Refractory Congestive Heart Failure

ARSHED A. QUYYUMI, DONALD WAGSTAFF, and THOMAS R. EVANS

Invasive hemodynamic measurements were made in 10 supine patients with chronic refractory congestive heart failure (CHF) before and after oral administration of a new arteriolar vasodilator, endralazine. With the 10 mg dose, substantial afterload reduction occurred, with increases in cardiac and stroke volume indexes of 56 and 42%, respectively, and a concomitant reduction in systemic resistance. A 5 mg dose produced similar but slightly less marked changes, with a small decrease in mean arterial pressure. There were no changes in right-sided cardiac pressures. Peak effect of the drug occurred 4 hours after the dose, and the effect was maintained for 8 hours. Endralazine, a structural analog of hydralazine, has a similar hemodynamic profile, but it is free from immunologic side effects and has a smaller dose range. This makes it a useful and safe drug in the management of CHF.

1358 Exercise Intolerance in Patients With Chronic Left Heart Failure: Relation to Oxygen Transport and Ventilatory Abnormalities

JOHN R. WILSON and NANCY FERRARO

Circulatory, metabolic, and ventilatory responses to maximal and submaximal symptom-limited exercise were studied in 13 patients with chronic stable heart failure. Maximal exercise was sustained 6.5 ± 0.6 minutes (mean ± standard error of the mean) and increased minute oxygen consumption ($\dot{V}O_2$) to 940 ± 65 ml/min, whereas submaximal exercise was sustained for 15.4 ± 2.3 minutes and increased $\dot{V}O_2$ to 825 ± 49 ml/min (both $p < 0.01$ compared with maximal exercise). Both exercise protocols were terminated because of fatigue and both were associated with reduced cardiac output relative to $\dot{V}O_2$, marked systemic oxygen extraction (80 ± 2% maximal versus 78 ± 2% submaximal) and similarly elevated blood lactate concentrations (37 ± 4 mg/dl maximal versus 36 ± 4 mg/dl submaximal), suggesting inadequate oxygen delivery to working muscle. Minute ventilation during both types of exercise was also more than twice normal relative to carbon dioxide production. During submaximal exercise, dyspnea was noted in only 3 patients despite these ventilatory abnormalities. During maximal exercise, dyspnea was noted in 11 patients but did not force termination of exercise or preclude achievement of marked systemic oxygen extraction and lactate production. These data suggest that patients with chronic stable cardiac failure are limited during both maximal and submaximal exercise primarily by inadequate oxygen transport to working muscle.

1364 Hemodynamic Effects of Dibutyryl Cyclic AMP in Congestive Heart Failure

SHINOBU MATSUI, EIJI MURAKAMI, NOBORU TAKEKOSHI, JIRO EMOTO, and MUNETOSHI MATOBA

In this study the hemodynamic effects of dibutyryl cyclic AMP (DBcAMP) were evaluated in patients with congestive heart failure (CHF). In 11 patients with CHF hemodynamic variables were investigated before and after infusion of various doses of DBcAMP at a rate of 0.025 to 0.2 mg/kg/min (0.14 ± 0.077 mg/kg/min mean ± standard deviation). DBcAMP reduced total systemic vascular resistance index, pulmonary arterial end-diastolic pressure, and mean arterial blood pressure. Cardiac index and heart rate were increased. The increase in cardiac index was accompanied by a proportional decrease in total systemic vascular resistance index. Left ventricular performance was improved in 8 patients. The incremental doses of DBcAMP (0.05, 0.1, and 0.2 mg/kg/min) caused dose-related hemodynamic changes. These results suggest that DBcAMP has powerful vasodilating effects on resistance vessels in patients with CHF; hence, it can be a useful vasodilating agent for the treatment of CHF.

THERAPY

1369 Pharmacokinetic and Pharmacodynamic Effects of Diltiazem

MARK S. SMITH, CHACKO P. VERGHESE, DAVID G. SHAND, and EDWARD L. C. PRITCHETT

The pharmacokinetic and pharmacodynamic features of diltiazem were studied in 8 patients after intravenous (20 mg over 10 minutes), single oral (60 or 90 mg), and repeated oral administration (60 or 90 mg every 6 hours). Plasma levels decreased triexponentially after intravenous administration, with a half-life similar to that after oral diltiazem. The time versus concentration curve after oral diltiazem showed 2 peaks, suggesting enterohepatic recirculation. The kinetic effects or oral diltiazem were nonlinear. With repeated doses, there was significant accumulation of diltiazem and its metabolite, and there was an increase in apparent bioavailability. While minimal changes occurred in heart rate and blood pressure, there was significant prolongation of the P-R interval.

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CONTENTS

VALVULAR HEART DISEASE

1375 Prevalence of Submitral (Anular) Calcium and Its Correlates in a General Population-Based Sample (The Framingham Study)

DANIEL SAVAGE, ROBERT J. GARRISON, WILLIAM P. CASTELLI, PATRICIA M. McNAMARA, SANDRA J. ANDERSON, WILLIAM B. KANNEL, and MANNING FEINLEIB

To obtain epidemiologic information on submitral calcium, 2,069 subjects in the original Framingham Study cohort (mean age 70 ± 7 years) and 3,625 of the offspring of the cohort and their spouses (mean age 44 ± 10 years) with adequate echocardiograms were evaluated. Submitral calcium was detected in 162 (2.8%) of the 5,694 subjects; >90% of the subjects with such calcium came from the 40% of the study group >59 years of age. Women were more than twice as likely to have such calcium as men. Age in both sexes, systolic blood pressure in men, and obesity in women were significantly and independently associated with submitral calcium. There was a 12-fold excess of atrial fibrillation in subjects with (20 of 162, 12%) compared with those without (53 of 5,532, 1%) submitral calcium.

1379 Left Ventricular Volume and Ejection Fraction Response to Exercise in Aortic Regurgitation

LYNNE L. JOHNSON, ERIC R. POWERS, WESLEY R. TZALL, JANET FEDER, ROBERT R. SCIACCA, and PAUL J. CANNON

Left ventricular (LV) ejection fraction (EF) and volumes were measured at rest and peak exercise using radionuclide techniques in 27 asymptomatic and 22 symptomatic patients with aortic regurgitation (AR). In the asymptomatic AR group both end-diastolic and end-systolic volumes decreased significantly during exercise, while EF increased. In contrast, for the symptomatic group as a whole end-diastolic volume did not change and end-systolic volume increased, while EF decreased or stayed the same. Within the symptomatic group there were 2 subgroups based on volume change: 7 of 22 had a decrease in end-diastolic and end-systolic volume (a response similar to the asymptomatic group), while 8 of 22 had an increase in both end-diastolic and end-systolic volumes during exercise. These data indicate that measurements of LV volume may be useful in differentiating symptomatic patients who are able to decrease end-systolic volume during exercise from those who develop worsening LV failure during exercise.

CARDIOMYOPATHY

1386 Atrial Systole and Left Ventricular Filling in Hypertrophic Cardiomyopathy: Effect of Verapamil

ROBERT O. BONOW, TERRI M. FREDERICK, STEPHEN L. BACHARACH, MICHAEL V. GREEN, PAMELA W. GOOSE, BARRY J. MARON, and DOUGLAS R. ROSING

The contributions of rapid diastolic filling and atrial systole to left ventricular (LV) filling volume were evaluated in 30 normal volunteers and 42 patients with hypertrophic cardiomyopathy (HC) using LV time-activity curves obtained by radionuclide angiography. Although the peak rate of rapid diastolic filling was normal in 81% of HC patients, the contribution of rapid filling to LV filling volume was reduced in 45% of patients and the contribution of atrial systole was increased in 40%. During oral verapamil therapy (320 to 560 mg/day), an increased rate of rapid filling was associated with an increase in the contribution of rapid filling to LV filling volume and a decrease in the contribution of atrial systole. During verapamil, the contribution of atrial systole was above normal in only 7% of patients. These data suggest that the hemodynamic risks associated with atrial fibrillation and loss of synchronized atrial contraction may be reduced during verapamil therapy.

1392 Regression of Myocardial Cellular Hypertrophy With Vasodilator Therapy in Chronic Congestive Heart Failure Associated With Idiopathic Dilated Cardiomyopathy

DONALD V. UNVERFERTH, JOHN P. MEHEGAN, RAYMOND D. MAGORIEN, BARBARA J. UNVERFERTH, and CARL V. LEIER

Thirty-three patients completed a 3-month study on the effect of 4 drug regimens (placebo, P; isosorbide dinitrate, I; hydralazine, H; and H + I). Resting central hemodynamic variables were determined and an endomyocardial biopsy was performed at baseline and after 3 months of continuous therapy; the myocardial cell diameter

Continued on page A51

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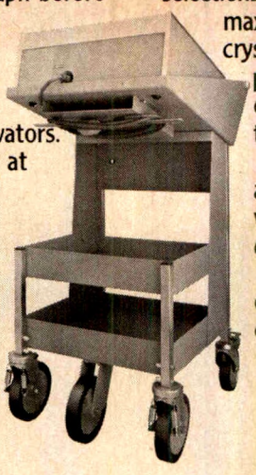

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[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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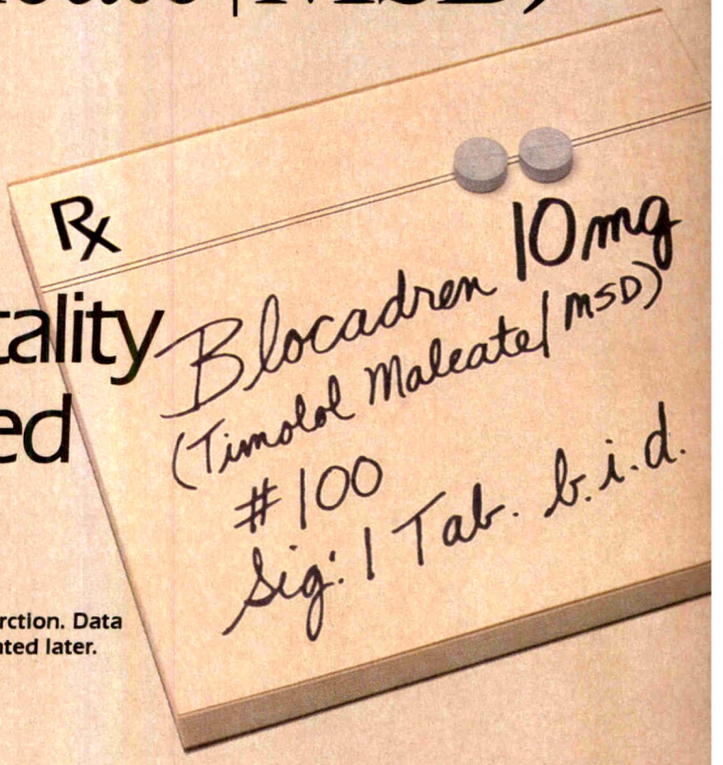

Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.

disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

BLOCADREN®
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CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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of 50 cells per biopsy was measured. The P group had no change in any measurements. The I and H + I groups had a significant decrease in pulmonary capillary wedge pressure and pulmonary vascular resistance. The H and H + I groups had a significant increase in cardiac index and a decrease in systemic vascular resistance and myocardial cell diameter. Chronic therapy of heart failure with I or H + I results in a persistent decrease in preload; chronic therapy with H and H + I effects a persistent augmentation in systolic function, a decrease in afterload, and an improvement in myocardial cellular morphology.

METHODS

1399 Comparison of Digital Intravenous Ventriculography With Direct Left Ventriculography for Quantitation of Left Ventricular Volumes and Ejection Fractions

SHARON L. NORRIS, ROBERT A. SLUTSKY, G. B. JOHN MANCINI, WILLIAM L. ASHBURN, GABRIEL GREGORATOS, KIRK L. PETERSON, and CHARLES B. HIGGINS, *With the technical assistance of* ELLEN EINSIDLER and WESLEY DILLON

Digital images of the left ventricle after central venous injection of contrast medium (digital intravenous ventriculography) were used to estimate left ventricular volumes and ejection function and compared with direct ventriculograms. Both end-diastolic volume ($r = 0.88$) and end-systolic volume ($r = 0.89$) correlated closely between the 2 techniques. Combining end-diastolic and end-systolic volume to define the relations between the 2 techniques yielded a high correlation ($r = 0.96$). It is concluded that area-length estimates of left ventricular volumes and ejection fraction can be accurately obtained from digital processing of fluoroscopic left ventricular images after intravenous injection of contrast medium.

1404 Regional Distribution of Pulmonary Blood Volume: An Index of Pulmonary Capillary Wedge Pressure Determined From Blood Pool Scintigraphy

TIMOTHY M. BATEMAN, RICHARD J. GRAY, LAWRENCE S. C. CZER, RONALD L. LEVY, MORGAN E. STEWART, MICHELE A. DeROBERTIS, DAVID E. BROWN, JACK M. MATLOFF, H. J. C. SWAN, and DANIEL S. BERMAN

Progressive redistribution of pulmonary blood flow to the lung apices occurs with increasing degrees of left ventricular failure. This study, using technetium-99m equilibrium blood pool scintigraphy, demonstrates that similar changes occur in the distribution of pulmonary blood volume, and correlates progressive changes in pulmonary blood volume toward the apex with progressive changes in pulmonary capillary wedge pressure (PCWP). Thirty patients being monitored with pulmonary artery balloon flotation catheters underwent imaging at the same time as PCWP determination. PCWP was compared with the average radioactive count density arising from apical (A) and basal (B) regions of interest within the right lung, expressed as an A/B ratio. Correlation between A/B and PCWP was strong for patients imaged erect in either the posterior ($r = 0.864$, $p = 0.001$) or left anterior oblique 45° position ($r = 0.842$, $p = 0.001$), and only slightly less so for patients imaged supine ($r = 0.678$, $p = 0.001$). Especially when imaging was performed with patients erect, an A/B ratio greater than unity identified with high sensitivity (100%) and specificity (83 to 88%) an abnormally elevated PCWP (>12 mm Hg). Moreover, directional changes in the A/B ratio reflected concomitant changes in PCWP after intervention. Thus, analysis of lung A/B radioactive count ratios obtained by equilibrium blood pool scintigraphy may be used to estimate PCWP.

EXPERIMENTAL STUDIES

1409 Sustained Limitation of Myocardial Necrosis 24 Hours After Coronary Artery Occlusion: Verapamil Infusion in Dogs With Small Myocardial Infarcts

DEREK M. YELLON, DAVID J. HEARSE, MILES P. MAXWELL, DAVID E. CHAMBERS, and JAMES M. DOWNEY

Studies were undertaken to ascertain whether verapamil infusion affords a sustained limitation of myocardial injury in the dog after a 24-hour period of coronary artery occlusion. Immediately after embolization radioactive microspheres were administered intraventricularly to define any area of myocardial underperfusion (zone at risk of infarction). Verapamil (0.005 mg/kg/min) was then administered and maintained for 24 hours during which time the dogs were allowed to recover from anesthesia. After 24 hours the dogs were killed and transverse myocardial sections (3 cm) were prepared. The resulting area of necrosis was visualized by tetrazolium staining, and

Continued on page A55

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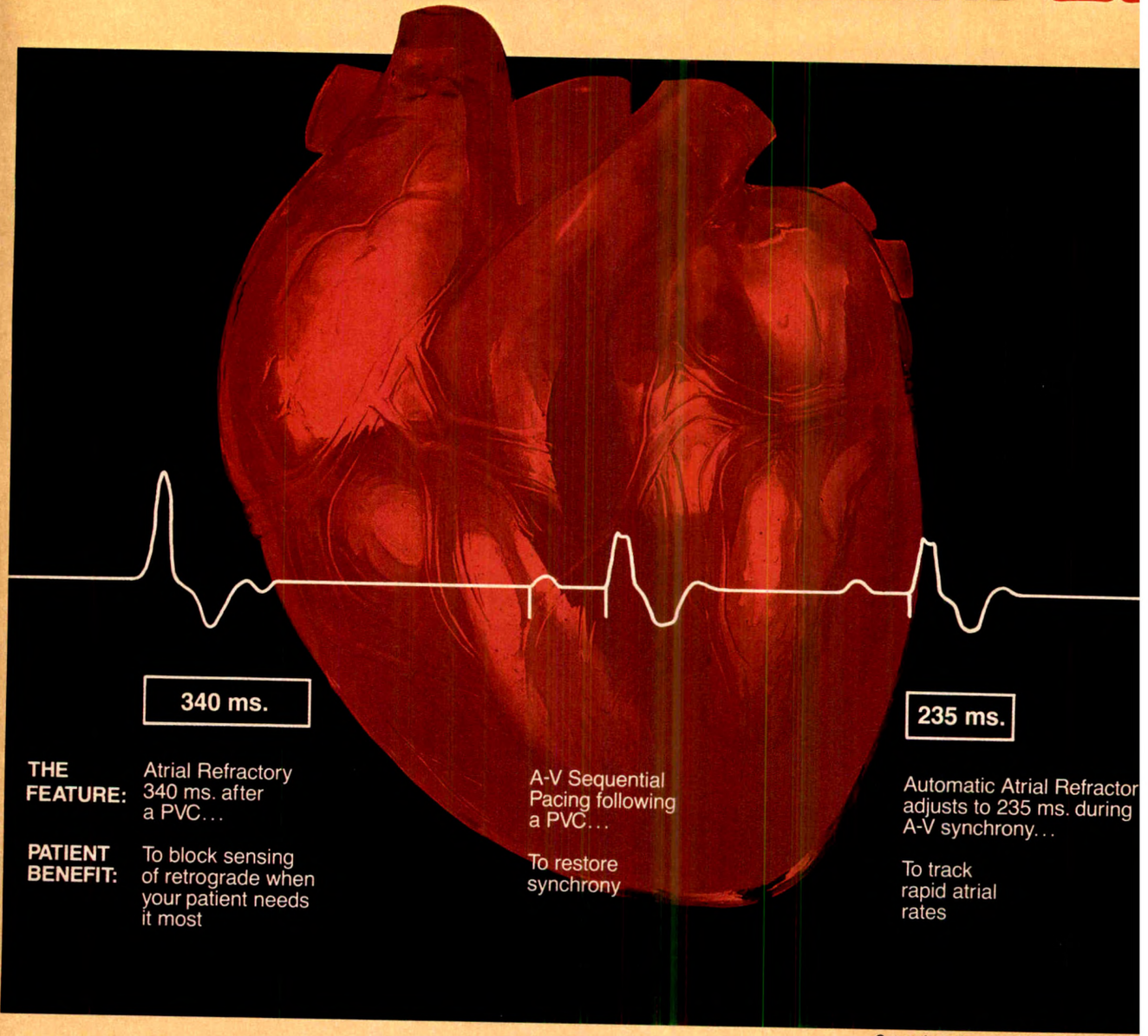

Currently undergoing U.S. Clinical Evalu

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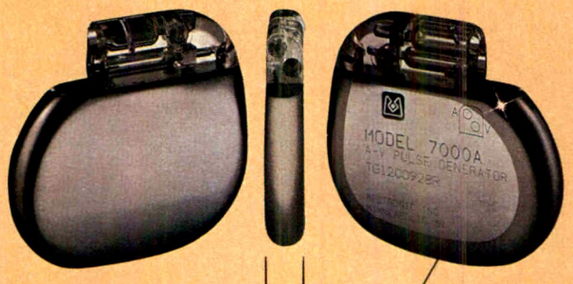
The most physiologic pacemaker.



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- **Superior Sensing Performance**
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Versatrax™ II Model 7000A Universal A-V Pacemaker

Intended Use

The Model 7000A universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy: Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

Electrosurgical Units: Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

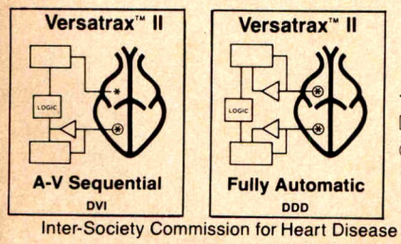
Defibrillation: Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



Inter-Society Commission for Heart Disease Research Code.

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risk zones were visualized by autoradiography. In the control heart, 62 ± 7% of the zone at risk deteriorated to necrotic tissue, whereas in the verapamil-treated group only 18 ± 4% of the tissue in the zone at risk became necrotic. Verapamil thus exerted a significant ($p < 0.001$) tissue-sparing effect that was sustained at least 24 hours after the onset of ischemia.

1414 Diastolic Synchronized Retroperfusion Versus Reperfusion: Effects on Regional Left Ventricular Function and Myocardial Blood Flow During Acute Coronary Occlusion in Dogs

JEAN C. FARCOT, ALAIN BERDEAUX, JEAN F. GIUDICELLI, JEAN P. VILAINE, and JEAN P. BOURDARIAS

The authors investigated the effects of 170 minutes of diastolic synchronized retroperfusion of the coronary sinus with arterial blood during 180 minutes of coronary artery occlusion on regional myocardial contractility (ultrasonic crystals) and blood flow (microspheres) in open-chest dogs. These effects were compared with those of 180 minutes of coronary occlusion and 170 minutes of anterograde reperfusion after 10 minutes of coronary occlusion in separate groups of dogs. Retroperfusion was able to almost restore transmural blood flow in the moderately ischemic zones and to raise it back to 47% of its preocclusion value in the severely ischemic zones with, in both zones, a favorable redistribution of flow toward the endocardium. Simultaneously, retroperfusion significantly improved segment length shortening in the moderately ischemic zones and significantly reduced the extent of paradoxical bulging in the severely ischemic zones. These partial recoveries in regional contractility and blood flow during retroperfusion were intermediate between those induced by 170 minutes of anterograde reperfusion and those of 180 minutes of coronary artery occlusion. Thus, in the presence of coronary artery occlusion, retroperfusion appears to exert a beneficial effect by improving both regional perfusion and function in the ischemic zones and may be proposed as a medical circulatory support to the jeopardized myocardium.

1422 Effects of Ortho-Iodo Sodium Benzoate on Acute Myocardial Ischemia, Hemodynamic Function, and Infarct Size After Coronary Occlusion in Dogs

ROBERT E. RUDE, JOHN TUMAS, MARCEL GUNST, ROBERT A. KLONER, LAURENCE W. V. DeBOER, and PETER R. MAROKO

Effects of ortho-iodo sodium benzoate (OISB), which decreases the affinity of hemoglobin for oxygen, thus enhancing potential tissue oxygen delivery, were tested in anesthetized dogs undergoing left anterior descending coronary artery (LAD) occlusion. Intravenous OISB reduced epicardial S-T segment elevation 15 minutes after LAD occlusion, while normal saline solution did not affect this index of ischemia. In 34 dogs, infarct size was assessed after death or killing 8 to 24 hours after LAD occlusion, and was 29% less in dogs that had received OISB before LAD occlusion. In a third group, OISB infusion 15 minutes after LAD occlusion decreased epicardial S-T segment elevation as well as heart rate, left ventricular dP/dt, and cardiac output, while a similar volume of normal saline solution had no effect on these variables. Thus, both acute myocardial ischemic injury and ultimate infarct size are reduced when OISB is infused before occlusion, and OISB also reduces ischemic injury when its administration is begun 15 minutes after LAD occlusion.

1428 Relation of Immediate and Delayed Thallium-201 Distribution to Localization of Iodine-125 Antimyosin Antibody in Acute Experimental Myocardial Infarction

BAN AN KHAW, WILLIAM STRAUSS, GERALD M. POHOST, JOHN T. FALLON, HUGO A. KATUS, and EDGAR HABER

Thallium-201 (Tl-201) is believed to be taken up by viable myocardium. Therefore, T1-201 distribution in acute experimental myocardial infarction was compared with cardiac-specific antimyosin Fab (AM-Fab) localization, a specific marker of myocyte necrosis, and with relative microsphere-determined regional myocardial blood flow. Our study showed that immediate (5 minutes) T1-201 distribution in experimental myocardial infarction is directly proportional to regional blood flow ($r = 0.971$) but is inversely exponentially related to iodine-125–AM-Fab uptake. On the other hand, delayed T1-201 distribution showed an inverse linear relation to AM-Fab uptake ($r = -0.935$ and -0.828). These relationships indicated that early T1-201 distribution reflected regional blood flow, whereas delayed T1-201 distribution demarcated viable myocardium, which is confirmed by the lack of AM-Fab uptake.

Continued on page A59

A THERAPEUTIC STEP AHEAD

LOPID®
(gemfibrozil)

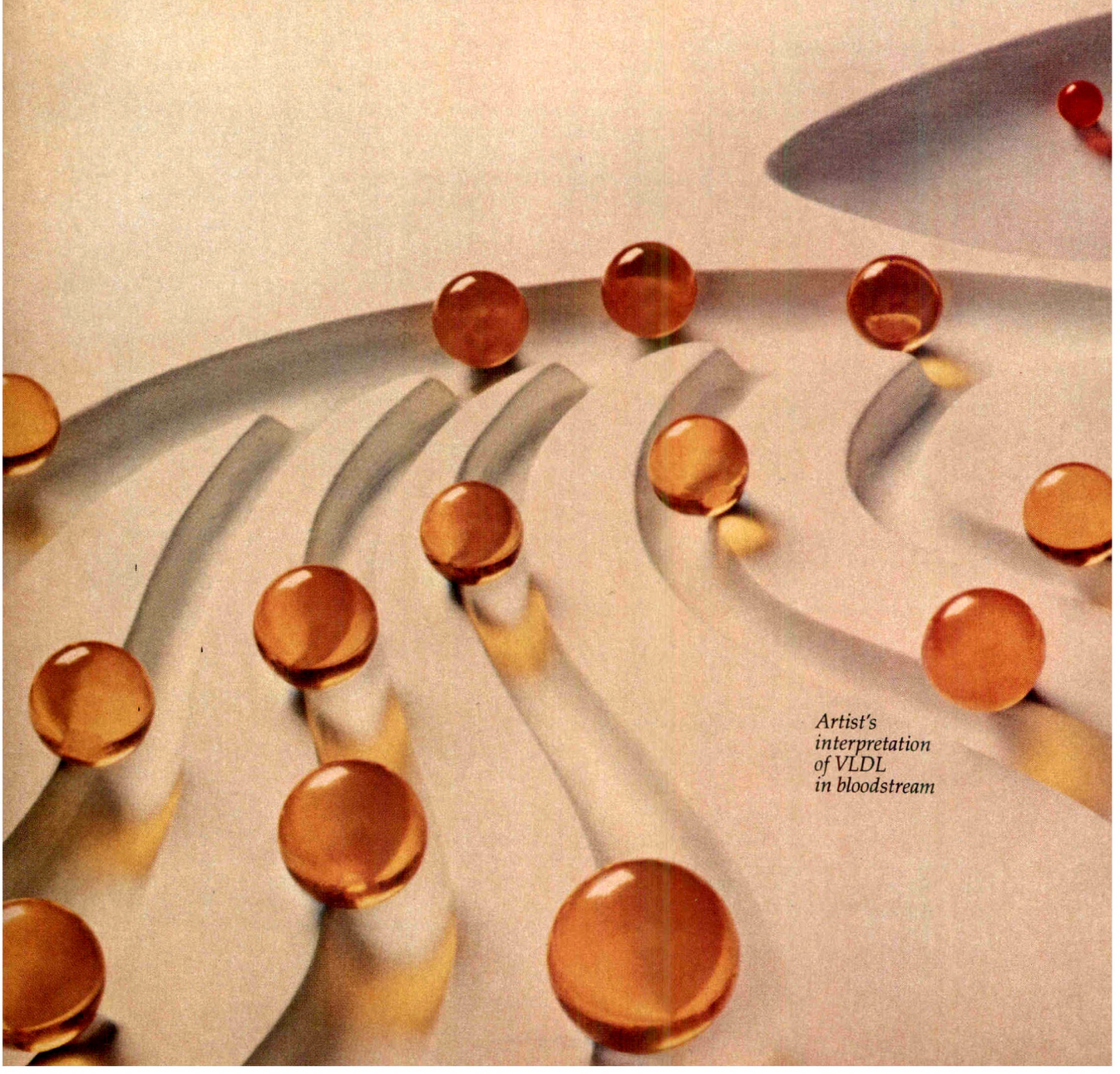
MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

Favorably regulates the balance of lipid fractions in certain dyslipidemias:

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent cholesterol-rich LDL (very-low- and low-dens lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transpo cholesterol to the liver for catabolism and excretion)

LOPID is indicated for treatment of adult patients with very high serum triglyceride leve (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

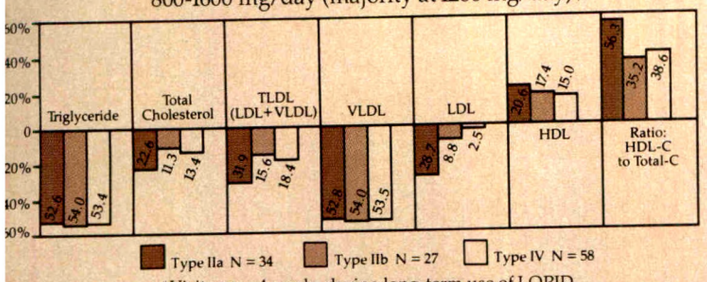


Artist's interpretation of VLDL in bloodstream

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.

†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:

1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

LOPID® 300-mg capsules

(gemfibrozil)

PARKE-DAVIS

Please see following pages for brief summary of prescribing information.

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LOPID®
(gemfibrozil)
A LIPID REGULATOR

LOPID® (gemfibrozil) Capsules

Before prescribing, please see full prescribing information.
A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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PD-56-JA-1333-P-1 (11-82)

CONTENTS

1433 Nature of "Residual Fast Channel" Dependent Action Potentials and Slow Conduction in Guinea Pig Ventricular Muscle and Its Modification by Isoproterenol

MAKOTO ARITA, TATSUTO KIYOSUE, MASAHIRO AOMINE, and SUNAO IMANISHI

The nature of "residual fast channel" dependent action potentials and conduction was studied in guinea pig ventricular papillary muscle in which the resting potential was reduced to 58 ± 1 mV in high K^+ (16.7 m*M*) Tyrode's solution, with or without isoproterenol (0.1 μM). In the absence of isoproterenol, the action potential had a slur on the upstroke and the maximum rate of rise ($\dot{V}_{max}$) was composed of 2 separable peaks: the early large (32 ± 7 V/s, $\dot{V}_{max,fast}$) and the late small (10 ± 2 V/s, $\dot{V}_{max,slow}$) ones. Conduction velocity ranged from 30 to 35 cm/s. $\dot{V}_{max,fast}$ was selectively depressed by tetrodotoxin (1 μM) and $\dot{V}_{max,slow}$ by l-verapamil (1 μg/ml), indicating that the impulses were transmitted through incompletely inactivated ("residual") fast channels. Lidocaine (2 μg/ml) depressed $\dot{V}_{max,fast}$ with reduction of conduction velocity to about 20 cm/s just before the conduction block. Isoproterenol quadrupled $\dot{V}_{max,slow}$ but decreased $\dot{V}_{max,fast}$. As a result, the $\dot{V}_{max,slow}$ overrode the $\dot{V}_{max,fast}$ without change in the conduction velocity. Isoproterenol produced rate-dependent shortening in action potential duration with rate-independent shortening of postexcitation refractoriness, thereby resulting in a significant shortening in the effective refractory period at faster rates (0.5 and 0.9 Hz). Results suggest that the "residual fast channel" could produce "slow conduction" and that the ionic channels (fast or slow) responsible for the slow conduction may alternate according to local concentrations of tissue catecholamines.

1441 Vessel Wall Arachidonate Metabolism After Angioplasty: Possible Mediators of Postangioplasty Vasospasm

ANDREW CRAGG, STANLEY EINZIG, WILFRIDO CASTANEDA-ZUNIGA, KURT AMPLATZ, JAMES G. WHITE, and GUNDU H. R. RAO

Vasospasm is a serious complication of angioplasty. The investigators postulated that arterial dilatation might interfere with vessel wall arachidonate metabolism and thus predispose the vessel to spasm. They found that balloon angioplasty of canine carotid arteries significantly impaired local production of the vasodilating prostaglandins PGI_2 and PGE_2 while augmenting production of the lipoxygenase product of arachidonate metabolism, 12L-hydroperoxy-5,8,10,14-eicosatetraenoic acid (HPETE), a potent vasoconstrictor. Thus, damage to the vessel wall during angioplasty alters local arachidonic acid metabolism and may contribute to vasospasm in certain cases.

1446 Cryosurgery of the Fetal Ductus Arteriosus

PAGE A. W. ANDERSON, FREDERICK B. ASKIN, and MARCOS J. PUPKIN

Cryosurgery of the fetal ductus arteriosus, a new approach to altering the function of the neonatal ductus arteriosus, is assessed. Cryosurgical treatment was performed in 5 fetal lambs (gestational age 127 ± 8 days ± 1 standard deviation) and sham treatment in 6 fetal lambs (gestational age 128 ± 5 days). After birth, all the cryotreated lambs had a patent ductus arteriosus while all the control lambs had a closed ductus arteriosus. Histologic evaluation demonstrated the media of the cyotreated ductus arteriosus to have calcification, bland necrosis, and ganglion cell necrosis. These findings suggest that cryosurgery may be a useful technique for maintaining ductus arteriosus patency.

1451 Coronary Constriction by Leukotriene C_4, D_4, and E_4 in the Intact Pig Heart

DAVID EZRA, LILLIE BOYD, GIORA FEUERSTEIN, and ROBERT E. GOLDSTEIN

Leukotrienes are vasoactive metabolites of arachidonic acid that increase during inflammatory reactions and anaphylaxis. To test effects of leukotriene C_4, D_4, and E_4 on coronary vessels, coronary blood flow, arterial pressure, left ventricular end-diastolic pressure, and heart rate were measured after bolus injection of 0.1 to 3 μg of each leukotriene into a coronary artery in 8 open-chest pigs. Each leukotriene produced a marked, dose-related decrease in coronary blood flow within 30 seconds of injection. Three micrograms of each leukotriene produced the following maximal decreases: $C_4 = 80 \pm 9\%$, $p < 0.001$; $D_4 = 81 \pm 3\%$, $p < 0.001$; $E_4 = 64 \pm 12\%$ $p < 0.005$. In several instances electrocardiographic signs of focal myocardial ischemia were recorded. Significant elevation of left ventricular end-diastolic pressure was observed after the large doses (1.0 and 3.0 μg) of leukotriene C_4 and D_4. This study shows that leukotrienes are extremely potent coronary constrictors for the in situ heart. This action may have deleterious consequences on myocardial perfusion when inflammatory processes and anaphylaxis lead to increased production of leukotrienes.

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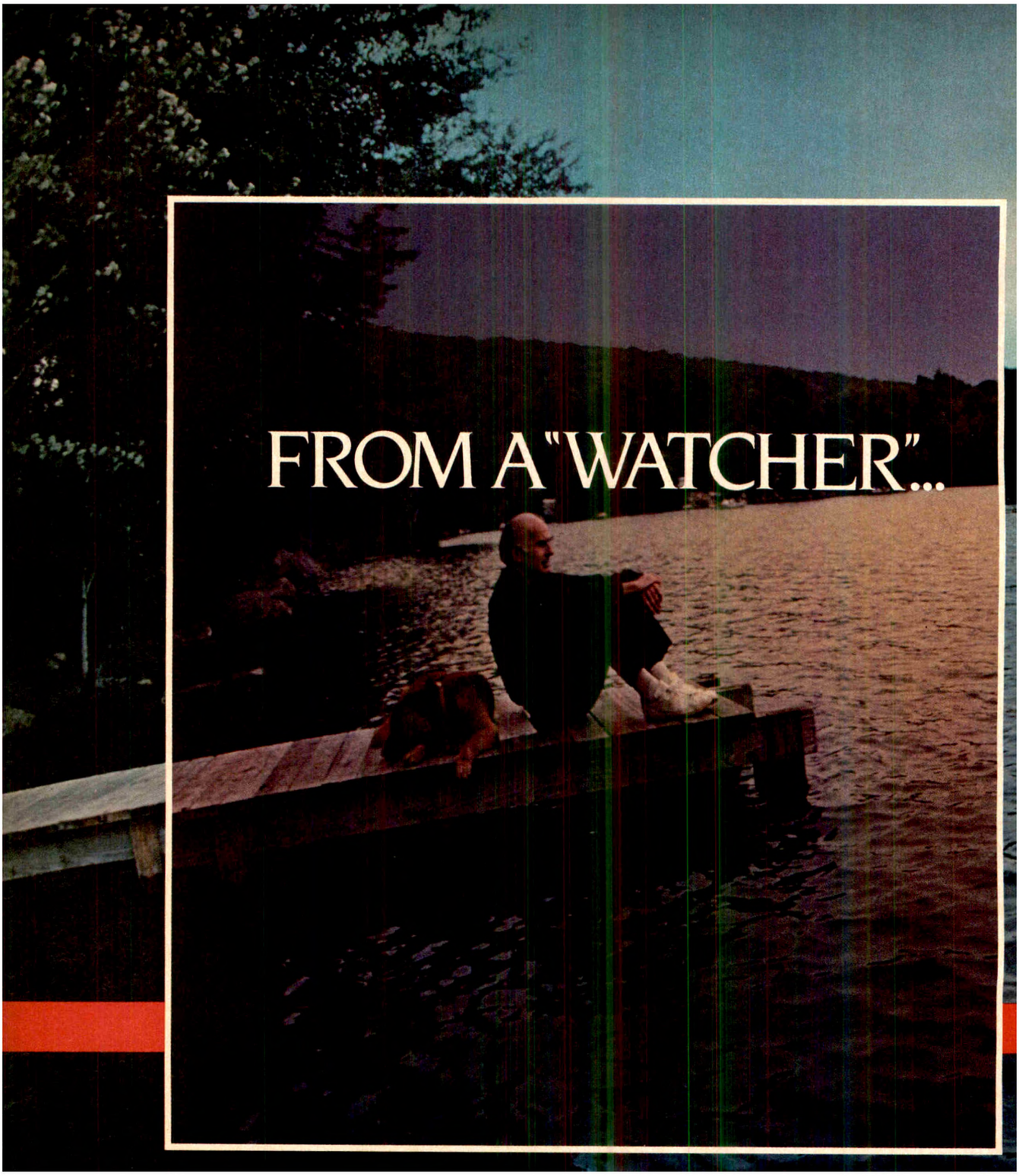
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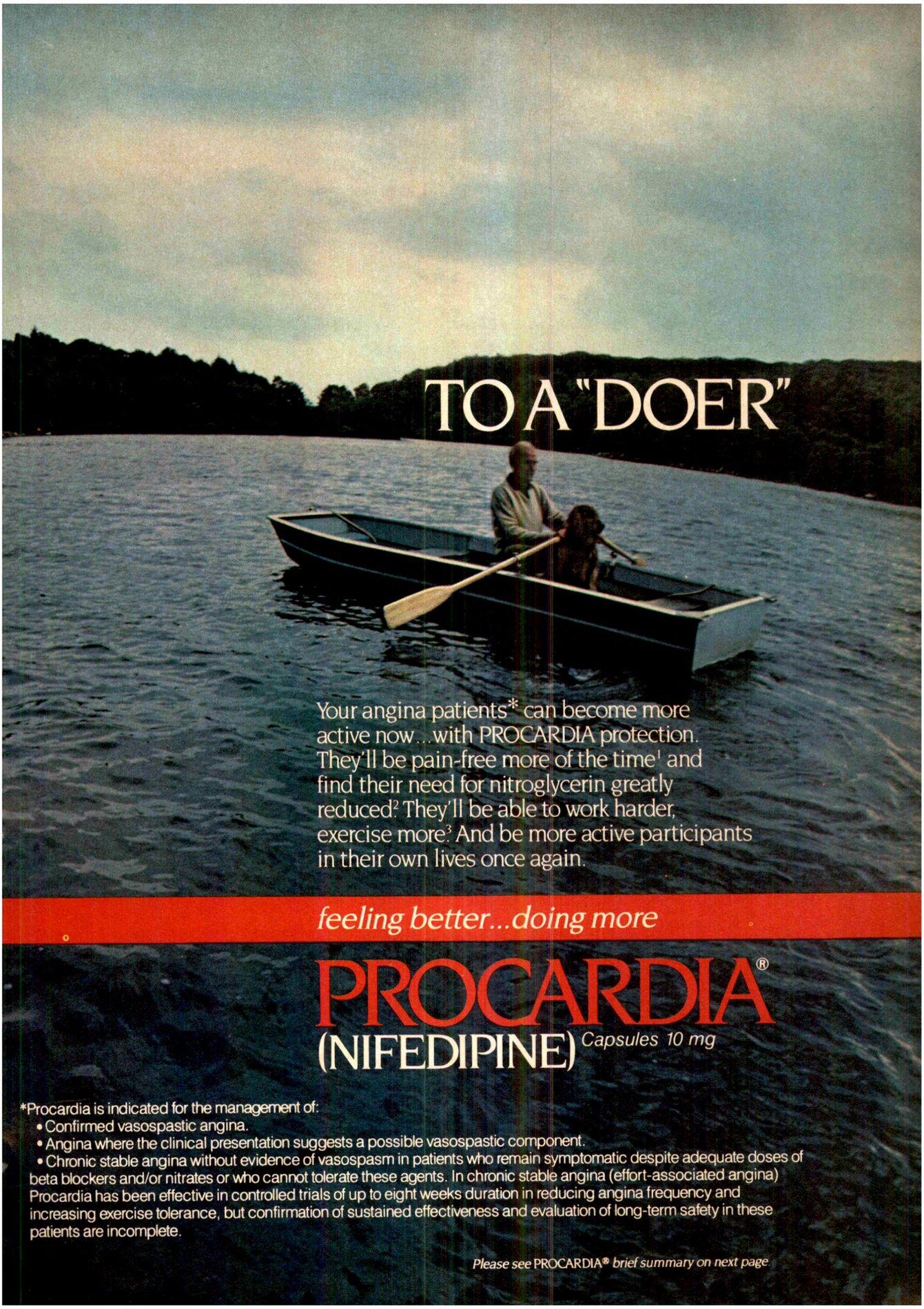

*Procardia is indicated for the management of:

- Confirmed vasospastic angina.
- Angina where the clinical presentation suggests a possible vasospastic component.
- Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) Procardia has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA® *brief summary on next page.*

feeling better...doing more

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

–Usual effective dosage is 30-60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.

BRIEF SUMMARY
PROCARDIA® CAPSULES For Oral Use
(nifedipine)

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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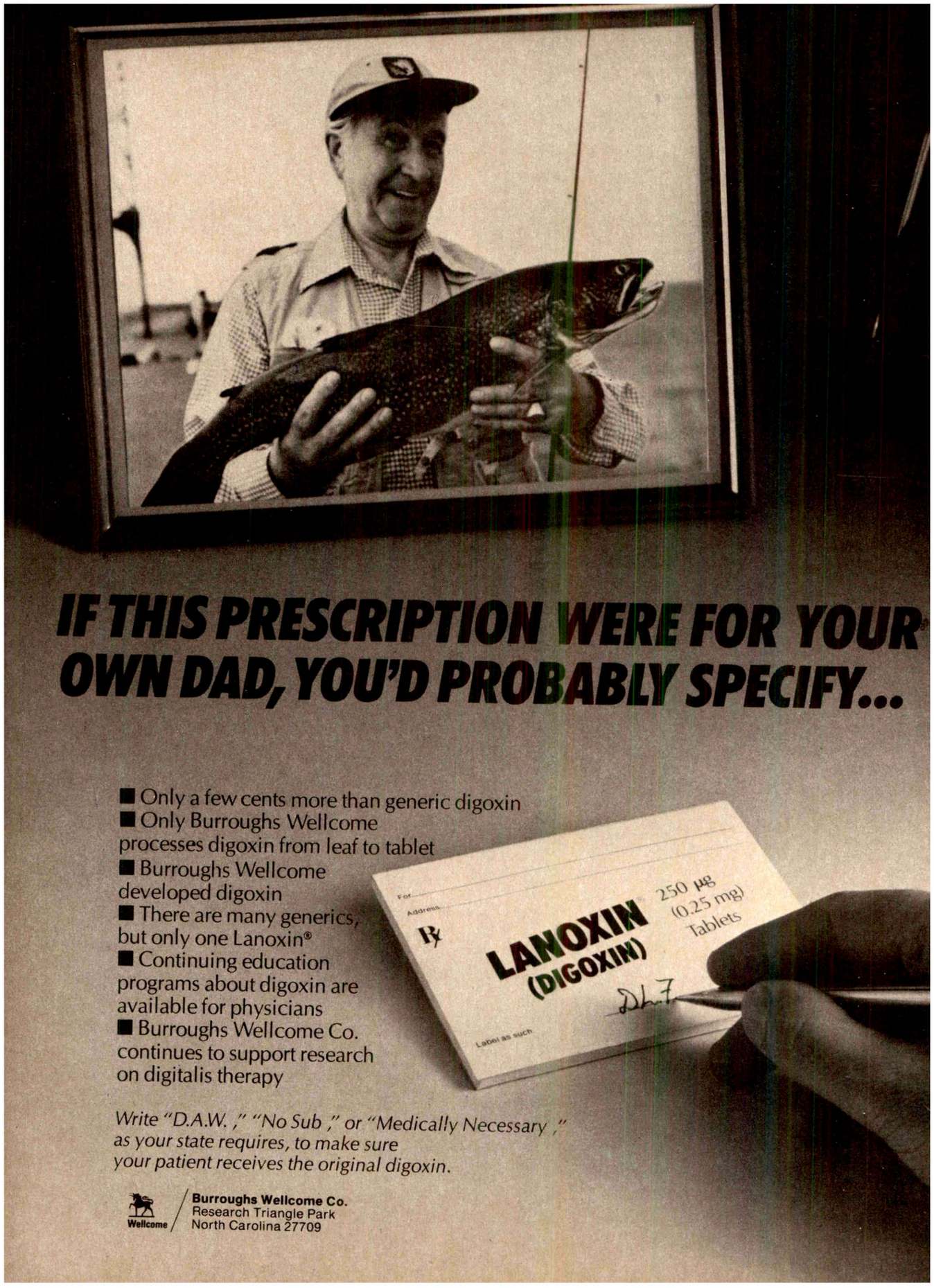
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NUMBER 8

CORONARY HEART DISEASE

Effects of Discontinuing Maintenance Digoxin Therapy In Patients With Ischemic Heart Disease and Congestive Heart Failure in Sinus Rhythm

MIHAI GHEORGHIADE, MD and GEORGE A. BELLER, MD

To evaluate the importance of oral maintenance digoxin therapy in chronic congestive heart failure (CHF), 24 patients in sinus rhythm on maintenance digoxin for documented CHF were studied prospectively on and off the drug. The average duration of therapy was 39 months (range 2 to 180). All 24 patients had documented coronary artery disease (CAD): 22 were in New York Heart Association functional class III and 2 in class II. Twenty-one patients (88%) were receiving diuretic or vasodilator therapy, or both, before digoxin discontinuance. At 1 month off digoxin and with no increase in doses of other medications excepting minor increases in antianginal therapy in 2 patients, no difference was observed in the group as a whole in symptoms, resting heart rate, arterial blood pressure, physical findings, weight, cardiothoracic ratio, radiographic signs of pulmonary congestion, radionuclide left ventricular ejection fraction (LVEF), duration of symptom-limited treadmill exercise (14 patients), or CHF score, compared with evaluation during maintenance digoxin therapy. Similar results were obtained in a subgroup of 9 patients with a resting LVEF <0.35 (0.27 ± 0.02; mean $\pm$ standard error of the mean). Six patients had a decrease and 5 patients an increase in LVEF of ≥ 0.05 units after cessation of digoxin. Off digoxin, the CHF score increased by only 1 point in 2 patients, but also decreased in 2 patients. Thus, in this study population comprised of patients with CAD with documented CHF, most of whom were receiving diuretics or vasodilators, or both, digoxin withdrawal had no adverse clinical or hemodynamic effects.

Although digitalis glycosides were introduced for treatment of cardiac maladies almost 200 years ago, controversy persists regarding the effectiveness and worth of the drug in the treatment of congestive heart failure (CHF). There is no doubt that cardiac glycosides are highly effective in controlling the ventricular response in the presence of atrial fibrillation. Previous work has shown that various digitalis preparations can improve cardiac performance when the drug is administered acutely under various conditions and indexes of myocardial contractility are measured.[1–3] Despite the demonstration of myocardial inotropic stimulation with short-term administration, controversy persists concerning the clinical and hemodynamic effects of chronic digitalis administration in patients with chronic coronary artery disease (CAD) in sinus rhythm with or without CHF.

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Given the fact that toxic manifestations of digitalis therapy comprise some of the most prevalent adverse drug reactions encountered in clinical practice,[4] it is disturbing that precise knowledge regarding which patients benefit from this drug and which do not is still lacking. The present study prospectively evaluates clinical and hemodynamic effects of digoxin discontinuance in patients with sinus rhythm with a clearly documented history of chronic CAD and CHF. We sought to evaluate not only alteration in symptoms after discontinuance of the drug but also changes in left ventricular function and exercise capacity. The major difference in study design from previous studies of digitalis withdrawal is that most patients in the present investigation were maintained on diuretic or vasodilator drugs, or both, during the period off digoxin. Also, the group was rather homogeneous in that all had CHF secondary to CAD.

Methods

Patient population: One hundred fourteen patients receiving maintenance digoxin were evaluated for possible inclusion into the study. Of these, 87 patients were excluded from participation in the trial for a variety of reasons including chronic atrial fibrillation in 26, no evidence of CHF or unclear indications for initial digitalization, or both, in 12, poorly documented history of CHF in 24, digitalization for CHF in the setting of acute myocardial infarction in 10, no CAD in 5, and subtherapeutic plasma digoxin levels in 10. The remaining 27 patients had CAD with documented previous myocardial infarction and all were studied prospectively. Of these, 2 patients were unable to complete the protocol. One patient, an 85-year-old man with a documented history of CAD, died suddenly 3 weeks after digoxin discontinuance. Before his death, no signs or symptoms consistent with worsening of CHF were evident. A second patient did not return for the 1 month follow-up visit but clinically his condition was stable off digoxin. A third patient had an unexpected plasma digoxin level of 0.9 mg/ml 1 month after allegedly discontinuing the drug. He subsequently admitted to resuming digoxin despite instructions to the contrary, and thus had to be eliminated from the study. Of the remaining 24 patients completing the protocol, all were men. Their mean age was 60 years (range 42 to 80). No patient had a history of atrial tachyarrhythmias.

The indication for initiating long-term digoxin therapy in all 24 patients was the presence of clinical or radiographic evidence of CHF, or both. At initial digitalization, 13 patients related symptoms of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea, and exhibited signs of sinus tachycardia, jugular venous distention, pulmonary rales, and an S_3 gallop. They demonstrated radiographic evidence of CHF such as cardiomegaly, pulmonary venous hypertension, interstitial edema, alveolar edema, or pleural effusion. In the remaining 11 patients, digitalization was prompted by symptoms and/or signs and/or radiographic findings of CHF but not all 3 as in the other 17 patients.

Twenty-two patients were in New York Heart Association functional class III and the remaining patients in class II. In no instance was CHF precipitated solely by recurring episodes of acute ischemia. All patients had chronic CHF. The duration of maintenance digoxin therapy before discontinuation ranged between 2 and 180 months (average 39). Plasma digoxin levels were obtained 6 to 8 hours after the last digoxin dose and ranged from 0.8 to 2.2 ng/ml (1.2 ± 0.3 ng/ml, mean ± standard deviation). Figure 1 summarizes the serum digoxin data in the 24 patients who completed the protocol. All had therapeutic serum digoxin levels. Twenty-one patients (88%) were receiving diuretic or vasodilator therapy, or both, for CHF before digoxin withdrawal. This included furosemide therapy in 12 (mean daily dose 55 mg; range 20 to 80), hydrochlorothiazide in 8 patients (mean daily dose 50 mg; range 25 to 100), hydralazine therapy in 2 (mean daily dose 93 mg; range 40 to 200), oral isosorbide dinitrate therapy in 13 (mean daily dose 66.1 mg; range 40 to 120), and nitroglycerin ointment in 3 (4 inches daily). Dosages of diuretics and vasodilators for individual patients were derived from clinical assessment. Diuretic doses were increased to the level of dry weight status without excessive volume depletion. Vasodilator doses to maximal efficacy were guided by arterial blood pressure responses, and in the case of nitrates, avoidance of side effects such as headache and dizziness. A total of 20 patients (83%) were receiving diuretics and 16 (66%) vasodilators. Fourteen patients were receiving both diuretics and vasodilators and 2 patients were taking a long-acting nitrate preparation and another vasodilator.

Concurrent therapy for CHF or angina pectoris was not altered during the follow-up period except in 2 patients in whom the isosorbide dinitrate therapy was initiated because of symptoms consistent with worsening of angina pectoris. In these patients no worsening of CHF was observed before beginning nitrate therapy.

Informed consent was obtained for each patient for digitalis withdrawal after detailed explanation of the study protocol. While patients were still receiving maintenance digoxin therapy and before drug discontinuance, baseline studies were obtained and consisted of the following: a complete cardiovascular history, physical examination including measurement of body weight, a resting 12-lead electrocardiogram, a standard posteroanterior chest roentgenogram, a resting gated cardiac blood pool scan, and a symptom-limited treadmill exercise test. Serial exercise testing as a method of assessment was introduced midway into the study, and hence, only 14 consecutive patients were studied in this manner. Each patient was assigned a heart failure score which is based on symptoms, signs, and findings on chest roentgenography. For this scoring system, each of the following signs or symptoms was assigned 1 point: dyspnea on exertion, paroxysmal nocturnal dyspnea, sinus tachycardia, jugular venous distention, pulmonary end-inspiratory rales, an S_3 gallop, a cardiothoracic ratio >0.5, radiographic interstitial edema, alveolar changes, pulmonary venous hypertension, pleural effusion, and peripheral edema. Thus, the score assigned ranged from zero, which reflected an absence of the 12 variables listed above, to a maximal score

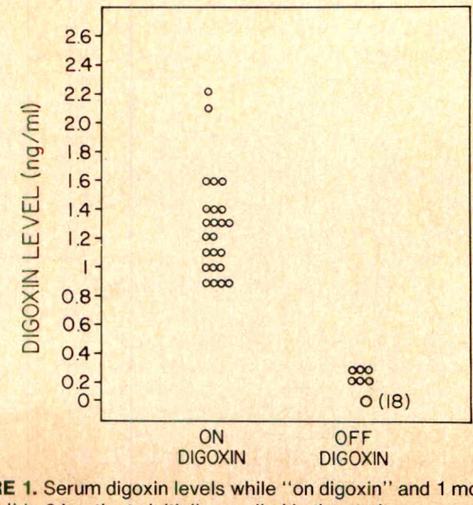

FIGURE 1. Serum digoxin levels while "on digoxin" and 1 month "off digoxin" in 24 patients initially enrolled in the study.

TABLE I Heart Rate (HR), Blood Pressure, Body Weight, and Exercise Tolerance Before and After Digoxin Discontinuance

	On Digoxin	Off Digoxin
HR (beats/min)	75 ± 2	73 ± 2
Blood pressure (systolic/diastolic)	122 ± 4/73 ± 2	125 ± 3/72 ± 2
Body weight (kg)	78.3 ± 2.7	78.2 ± 2.7
Exercise capacity (min)*	7.1 ± 1.2	7.8 ± 0.9

* Exercise testing conduction in 16 consecutive patients.

of 12, representing the presence of each of the listed findings.

Serum digoxin determination: The serum digoxin was measured by a standard commercial radioimmunoassay technique employing iodine-125-digoxin as the standard (Abbott Laboratories).

Chest roentgenography: In all instances, the cardiothoracic ratio was measured and the lung fields were evaluated for signs of pulmonary congestion by 2 radiologists interpreting the X-ray independently without knowledge of the patient's clinical status. Differences in interpretation were resolved by a third observer and the majority opinion prevailed.

Exercise test protocol: Maximal symptom-limited, graded exercise treadmill testing was conducted according to a modified Bruce[5] or National Institutes of Health protocol. In the modified Bruce protocol, exercise testing was initiated at 1 mph and 5% grade. Both speed and incline were increased every 3 minutes to 1.4 mph and 7% grade, 1.7 mph and 10% grade, 2.5 mph and 12% grade, 3.4 mph and 14% grade, 4.2 mph and 16% grade, and 5.0 mph and 18% grade. Employing the National Institutes of Health protocol, the treadmill was started at 2.2 mph and 0% grade. The speed was then held constant but the grade increased 2.5% every 2.5 minutes. The test was performed with the patient in the postabortive state. Because of the potential "training effect," each patient had 2 treadmill tests while on maintenance digoxin, and only the result from the second test was used for comparison with the exercise test after digoxin was withdrawn.

Radionuclide techniques: In vivo red blood cell labeling was accomplished by intravenous injection of 7.5 mg stannous pyrophosphate followed 20 minutes later by 25 mCi technetium-99m pertechnetate. A gamma camera (Ohio Nuclear Sigma 410; VIP 450 computer with dual floppy discs) was positioned over the patient's chest in a 50° left anterior oblique position. This maximized separation of the right and left ventricles. A computer program (Multi-Interval Cardiac Analysis Package) was used for both background subtraction and smoothing and edge detection and for setting the designated area of interest. Left ventricular ejection fraction was calculated by subtracting end-systolic counts from end-diastolic counts and dividing by the end-diastolic counts minus background counts. All radionuclide angiographic data was calculated without knowledge of the patient's clinical status or knowledge of the other quantitative measurements.

Follow-up studies: After completion of the baseline evaluation, the administration of digoxin was discontinued in all patients. All patients who had a baseline ejection fraction of <0.35 had the drug withdrawn while under observation in the hospital for a period of 10 days. These patients were evaluated on a daily basis for any clinical signs or symptoms consistent with cardiac decompensation. Each patient in the entire group was reexamined at 2 and 4 weeks after digoxin withdrawal, and monthly thereafter for an average of 4 months (range 2 to 8). At the 2-week visit, a complete cardiac history, physical examination, chest roentgenogram, and 12-lead electrocardiogram were again obtained. At the 1-month visit a chest roentgenogram and a 12-lead electrocardiogram only were repeated and another symptom-limited exercise test, a resting radionuclide ejection fraction, and plasma digoxin level were obtained. At each month thereafter, follow-up involved solely clinical and radiographic parameters.

Statistical analysis: Values are expressed as mean ± standard error of the mean. Comparison between baseline and digoxin withdrawal studies in individual patients were made using the paired t test, and comparison between groups was performed using analysis of variance.

Results

One month after digoxin withdrawal, no significant difference was observed in cardiac symptoms, resting heart rate, systolic, diastolic, or mean blood pressure, body weight, physical findings, cardiothoracic ratio, radiographic signs of pulmonary congestion, radionuclide ejection fraction, duration of symptom-limited treadmill exercise, or the heart failure score compared with the baseline evaluation gathered during chronic maintenance digoxin therapy.

Heart rate: As shown in Table I, the mean heart rate at rest was 75 ± 2 beats/min during digoxin therapy and 76 ± 2 beats/min after digoxin discontinuance, respectively. This difference was not statistically significant (NS).

Blood pressure: Digoxin withdrawal had no significant influence on mean systolic or diastolic blood pressure. Systolic and diastolic blood pressure was 122 ± 4 mm Hg and 73 ± 2 mm Hg, respectively, during maintenance digoxin and increased insignificantly to 125 ± 3 mg Hg and 72 ± 2 mm Hg at 1 month after digoxin discontinuance (Table I).

Body weight: As shown in Table I, mean weight was 78.3 ± 2.7 kg on digoxin and 78.2 ± 2.7 kg off digoxin (NS).

Cardiothoracic ratio: The cardiothoracic ratios in this group of patients before and after digoxin discon-

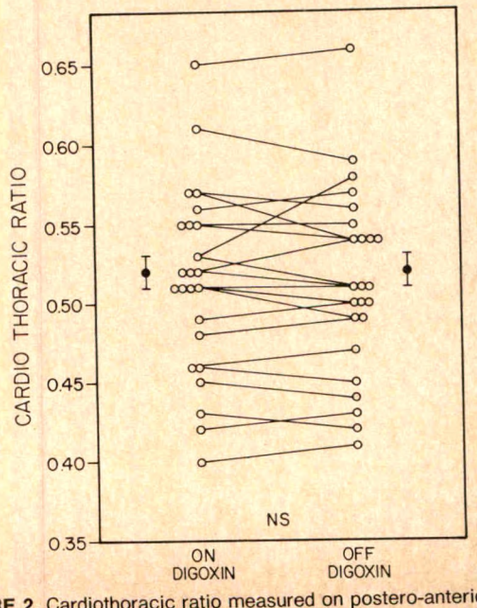

FIGURE 2. Cardiothoracic ratio measured on postero-anterior chest roentgenogram on and 1 month off digoxin. NS = not significant.

tinuance are shown in Figure 2. Most patients (67%) had cardiomegaly as defined by a cardiothoracic ratio >0.5. At 1 month of digoxin discontinuance, the cardiothoracic ratio was unchanged compared with the baseline measurements (0.53 ± 0.01 and 0.53 ± 0.01, respectively).

Left ventricular ejection fraction: Figure 3 summarizes left ventricular ejection fraction (LVEF) data in this group of patients. Both individual and mean values on and off digoxin are shown. The mean LVEF was 0.41 ± 0.03 during chronic maintenance digoxin therapy and was 0.41 ± 0.03 at 1 month of digoxin discontinuance. After digoxin withdrawal, no change in LVEF was observed in 15 patients, defined as an increase or decrease of ≥0.05 units. Six patients had a decrease and 3 patients showed an increase in LVEF of ≥0.05 units. The mean baseline LVEF before digoxin withdrawal in the 6 patients demonstrating a decrease in LVEF off digoxin was 0.45 ± 0.06, compared with 0.40 ± 0.03 in the remaining 18 patients who showed no change (n = 15) or an increase (n = 3) in ejection fraction after 1 month of digoxin discontinuance (NS). Thus, baseline LVEF was not significantly different in the 2 groups.

The heart failure score was 2.42 ± 0.50 on digoxin in the 6 patients who subsequently showed a decrease in LVEF, compared with 2.15 ± 0.30 in the 22 patients in whom LVEF increased or remained unaltered off digoxin (difference also was NS). Only 1 of the 6 patients demonstrating a decrease in LVEF off digoxin had a concomitant increase in heart failure score (by 1 point). A decrease in LVEF off digoxin did not correlate with a worsening of heart failure score. The mean cardiothoracic ratio in the 6 patients showing a decrease in LVEF off digoxin (0.50 ± 0.01) was not significantly greater than that in patients showing no change or a decrease in LVEF after drug discontinuance (0.52 ± 0.01). Thus, these 2 subgroups were comparable with respect to baseline heart size as judged by chest roentgenographic measurements.

Figure 4 shows that even when a subgroup of 9 patients with marked left ventricular dysfunction are analyzed separately (ejection fraction ≤0.35), no significant change was noted off digoxin (0.27 ± 0.02 versus 0.28 ± 0.02). Of these 9 patients, only 1 had a decrease >0.05 units in ejection fraction when digoxin was discontinued.

Exercise capacity: Serial treadmill exercise testing was conducted in 14 patients (Table I). There was no significant change in the duration of treadmill time between baseline and digoxin withdrawal states, 6.1 ± 0.8 and 7.2 ± 0.9 minutes, respectively. Off digoxin, the duration of symptom-limited treadmill time was increased in 6 patients, decreased in 1, and unchanged in the remaining 7. Baseline characteristics in the 14 patients undergoing treadmill testing were not significantly different from those in the remaining 10 patients.

Heart failure score: As shown in Figure 5, there was no significant difference in the derived mean heart failure score when baseline and digoxin withdrawal values were compared. The score was 2.1 ± 0.3 on digoxin and 2.1 ± 0.3 off digoxin (NS). The fact that the scores were relatively low to begin with reflected the compensated state these patients were in before withdrawal of the glycoside. Off digoxin, the heart failure score was unchanged in 20 patients and increased by 1 point in 2 patients. The heart failure score decreased by 1 point in 2 patients. The 2 patients who showed an increase in heart failure score off digoxin had an S_3 gallop while on digoxin, as compared with 3 of 25 patients with an unchanged or improved heart failure score. Decompensation in 1 of the 2 patients showing an increase in heart failure score can probably be attributed to discontinuance of maintenance diuretic or vasodilator drugs, or both, during the period off digoxin (Fig. 6). The second patient had resting sinus tachycardia 1

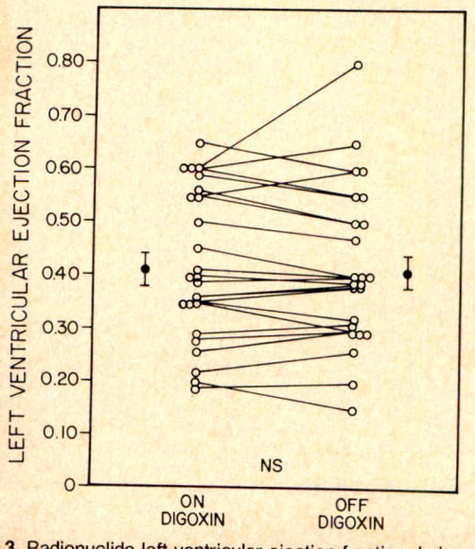

FIGURE 3. Radionuclide left ventricular ejection fraction during chronic maintenance digoxin therapy and at 1 month of digoxin discontinuance. NS = not significant.

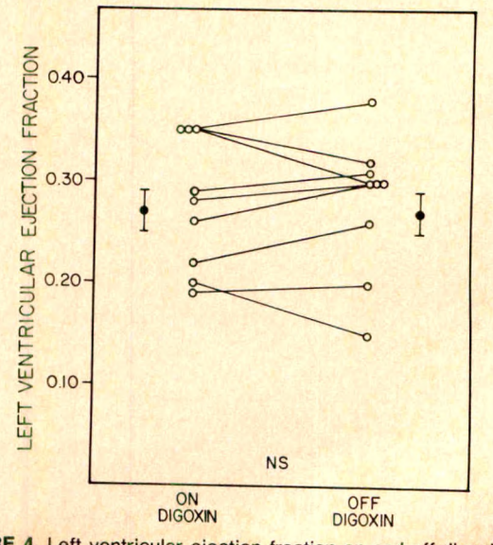

FIGURE 4. Left ventricular ejection fraction on and off digoxin in a subgroup of 9 patients with ejection fractions ≤0.35.

month off digoxin, but no other clinical or radiographic signs of CHF. The 1 point increase in heart failure score off digoxin in this patient was secondary to the increase in the sinus rate.

Discussion

The results of this study show that cessation of oral maintenance digoxin therapy in a group of 24 male patients in sinus rhythm with documented ischemic heart disease and compensated CHF had little adverse effects. Only 2 of the 24 patients demonstrated an increase in heart failure score after digoxin withdrawal. With digoxin discontinuance in the 24 patients, there was no gain in mean body weight, increase in heart size by radiographic criteria, or appearance of radiographic pulmonary vascular congestion. Exercise tolerance did not decrease in those patients undergoing serial testing. Likewise, in the group as a whole, no deterioration in resting LVEF was apparent off digoxin. Even when a subgroup of 9 patients with severely compromised left ventricular systolic dysfunction (mean LVEF 0.27) was analyzed separately, no worsening of clinical status or exercise tolerance or further decrease in ejection fraction could be detected. It must be emphasized that all these patients had chronic ischemic heart disease and most (88%) were receiving diuretic or vasodilator therapy or both concurrent with digoxin discontinuance. One potential hazard of discontinuing digoxin in patients with chronic heart failure is the emergence of supraventricular tachyarrhythmias. In this study, no such arrhythmias developed.

The indications for the initial digitalization were well documented in this study population. A potential criticism of this or similar studies is that digitalis therapy may not have been warranted in the first place. Interestingly, 36 of the 114 patients initially screened for the withdrawal protocol were receiving maintenance digoxin without any documentation of CHF or other accepted indications for digitalization. These patients would obviously have done well after digoxin discontinuance because they did not require the drug in the first place. None was included in the study group. In the present study, all patients had documented CHF by objective criteria. Patients were judged to be compensated at the time of digoxin withdrawal, explaining a rather low baseline heart failure score. On initial digitalization during decompensated CHF, the mean score for the group would have been higher.

For more than 100 years after the first description of the use of digitalis in the management of patients with edema by Withering[6] in 1758, the concept was held that digitalis was to be employed in the treatment of edema, particularly in the presence of atrial fibrillation. The teachings of McKenzie and Lewis in the early 1900s reinforced the recommendation that digitalis be used predominantly in atrial fibrillation. Not until the 1920s, based on the work of Christian,[7,8] Luten,[9] and Marvin,[10] was this view opposed and evidence presented that the drug was equally effective in CHF and sinus rhythm as in atrial fibrillation. The controversy persisted, and in 1939 Gavey and Parkinson[11] reported that digitalis produced similar but modest responses in nonrheumatic

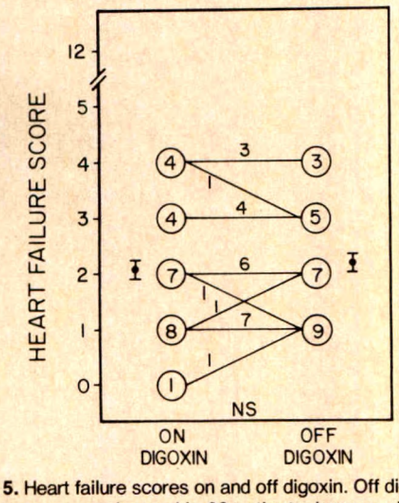

FIGURE 5. Heart failure scores on and off digoxin. Off digoxin, the heart failure score was unchanged in 20 patients, increased by 1 point in 2 patients, and decreased by 1 point in 2 patients. NS = not significant. Number of patients designated inside **circles**.

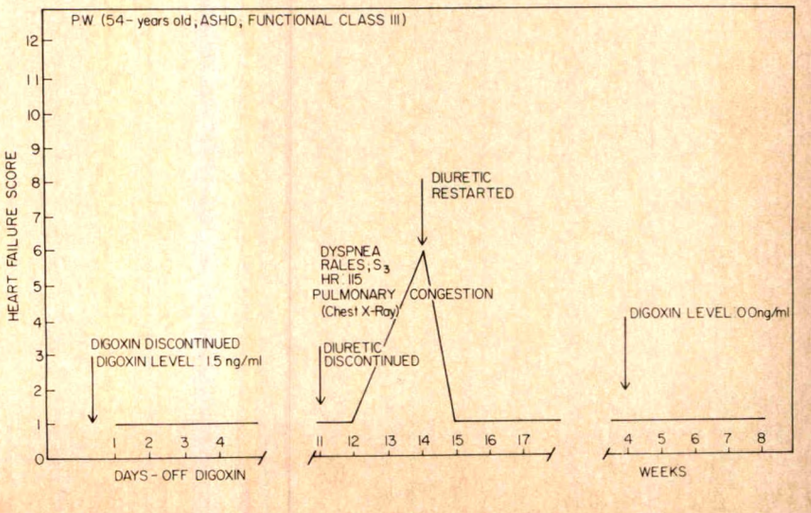

FIGURE 6. This patient did well for 11 days off digoxin, at which time the diuretic drug was withdrawn. Three days later, the patient presented with symptoms and signs of heart failure. When only the diuretic was restarted, the patient returned to the baseline compensated state. Digoxin was not reintroduced at any time. ASHD = arteriosclerotic heart disease; HR = heart rate.

patients whether they were in atrial fibrillation or in sinus rhythm. In their report, 16 patients in sinus rhythm who did not respond to digitalis did have a diuresis after the administration of a mercurial diuretic. The belief that digitalis was a highly effective drug in the treatment of CHF and sinus rhythm was reinforced by the emergence of hemodynamic studies in the 1940s.[12,13] Rader et al [14] concluded that most symptoms of CHF were a reflection of circulatory congestion and did not bear any relation to cardiac function. Removal of the congestive state with either digitalis or diuretics was associated with marked clinical improvement, whether or not the drugs altered intracardiac pressure or cardiac output. Although these studies demonstrated that inotropic cardiac stimulation was not required for relief of symptoms in most cases of CHF, the practice of cardiology changed little and digitalis remained the primary drug of choice for most patients with CHF.

Only recently have studies been undertaken to examine critically the efficacy of chronic maintenance digitalis therapy in the treatment of CHF.[15–25] With the advent of more potent diuretics and the demonstrated benefit of vasodilators in left ventricular unloading, the relative worth of digitalis in this multidrug approach is being reexamined. Starr and Luchi[15] withdrew digitoxin from elderly women who were in sinus rhythm. The results were entirely negative because neither patients nor investigators could distinguish between digitoxin treatment and control periods. Johnston and McDevitt[17] demonstrated that digitalis discontinuance in patients with normal sinus rhythm resulted in a 14% incidence of adverse effects. In their study, no objective hemodynamic or exercise parameters were evaluated and indications for the initial digitalization in the patient cohort were not described. Dall[18] and Krakauer and Petersen[21] showed that digoxin therapy could safely be discontinued in three fourths of elderly patients receiving the drug. Hull and Mackintosh[19] also reported that withdrawal of digoxin in patients with sinus rhythm did not produce any alterations in cardiovascular signs or symptoms. In these latter studies, there was also incomplete characterization of patients and lack of documentation of CHF. No serial hemodynamic or exercise data were presented.

In the study by McHaffie et al,[20] patients were first placed on oral furosemide, and after dry weight was achieved and edema resolved, exercise testing was performed to determine the benefit of oral digoxin added to the diuretic treatment. No evidence of symptomatic improvement or enhanced exercise tolerance could be detected when digitalis was added to the diuretic. No change in the cardiothoracic ratio was evident. Our results in a larger group of patients was comparable.

Other investigators have reached somewhat different conclusions. Fonrose et al[22] stopped digitalis therapy in a group of patients on a digitalis preparation for at least 1 year, with 50% requiring digoxin to be prescribed again within 3 to 21 days. The remaining 50% of the group were successfully maintained without the glycoside for periods of 4 months. In a placebo-control study reported by Dobbs et al[23] conducted in outpatients in whom a placebo was substituted for digoxin, 35% had a deterioration in their condition when digoxin was withdrawn. However, 28% had underlying atrial fibrillation. Of the patients whose condition deteriorated, 50% demonstrated improvement when digoxin was reintroduced. A pitfall of this study is that most data were obtained from questionnaires directed at eliciting changes in symptoms. Only a few patients demonstrated radiographic pulmonary congestion after withdrawal of digitalis. It is not clear which patients' condition deteriorated, those with sinus rhythm or those in atrial fibrillation, and the number of patients with atrial fibrillation in the group that had a relapse on placebo was not stated. The relation between deterioration and the type of underlying heart disease was not determined. Hence, no definitive conclusion regarding efficacy of digoxin therapy solely in patients with compensated CHF and sinus rhythm could be drawn. A common feature of the studies of Fonrose et al[22] and Dobbs et al[23] was that deterioration associated with digoxin withdrawal was manifested by increased salt and water retention. Decompensation might not have occurred if appropriate diuretic or vasodilator therapy, or both, had been maximized before digitalis discontinuance.

More recently, Arnold et al[24] studied only 9 patients during rest and after exercise on long-term digoxin therapy, after withdrawal of the drug, and 6 hours after readministration. All were in sinus rhythm. In this study, cessation of digoxin was associated with documented deterioration in left ventricular performance as indicated by a 13% decrease in mean cardiac index, a 24% decrease in stroke work index, and a 38% increase in pulmonary capillary wedge pressure. Worsening exercise hemodynamics were observed as well. With readministration of the drug, improvement was noted. A decrease in ejection fraction was noted in 7 of these 9 patients. This study included a rather small number of patients, and the variability of the hemodynamic changes in individual patients was significant. In fact, 4 of the 9 patients studied did not have a change in functional class after digoxin withdrawal. A major difference between Arnold's study and ours is that in the former only 3 patients had ischemic heart disease and only 3 patients were receiving vasodilators at the time of digitalis withdrawal. In the present study, all patients had ischemic heart disease with compensated CHF and were receiving diuretics or vasodilators, or both. Thus, differences in patient population could, in part, explain the difference in findings between Arnold's study and ours.

Lee et al,[25] in a controlled study, reported a benefit of oral digoxin compared with placebo in 56% of patients with chronic heart failure who were in sinus rhythm. Although most patients were receiving diuretics, only 24% were on vasodilators during placebo and digoxin study periods. In our study, 66% were receiving vasodilators at the time of digoxin withdrawal. This difference may perhaps account in part for the less beneficial effects of digoxin observed in our study. Also, all our patients had CHF secondary to ischemic heart disease

which was not the case in the group studied by Lee et al.[25] We confirm the observation of Lee et al of no change in LVEF when digoxin is discontinued.

Recently, Moss et al[26] and Bigger et al[27] suggested that chronic digitalis therapy after recovery from myocardial infarction may be an independent variable associated with increased mortality in patients with CHF, even when adjusted for relevant nondigitalis risk factor variables. The conclusions of these studies were that digitalis may increase the early postdischarge mortality of certain survivors of myocardial infarction. Our study population was comprised of patients with chronic ischemic heart disease. If digoxin has little salutary effect compared with diuretic and vasodilator therapy in these patients, caution should be exercised in choosing to put such patients on sustained maintenance therapy if an increased risk of sudden death exists, as suggested by these 2 reports.

From a review of the literature no definitive conclusion can be drawn concerning the efficacy of chronic digitalis therapy in patients with chronic ischemic heart disease.[28–38] In most instances, only a few patients were studied and many did not have CHF. Many studies investigated only the acute effects of intravenous digitalis. The hemodynamic improvement documented in these previous studies in patients with ischemic heart disease was slight to modest and can, for the most part, be attributed to enhanced contractility induced by the drug in normal segments. Comparison with vasodilators with regard to relative worth was not carried out. Raabe[39] showed that in acute myocardial infarction, intravenous digoxin showed no further hemodynamic benefit if nitroprusside was given first. Firth et al[40] studied 14 patients with coronary artery disease and compensated CHF. All were receiving nitrates or diuretics, or both, before digoxin administration. They found no significant effect of digoxin on ejection fraction at rest or at peak exercise. There was no effect on stroke volume or cardiac index, and digoxin did not prevent the exercise-induced increase in end-diastolic and end-systolic volume indexes in patients with an ejection fraction <0.5. No significant change in exercise tolerance was noted during digoxin therapy. Perhaps the lack of impressive improvement with digoxin in this series of patients is related to the fact that most were receiving vasodilators.

A limitation of our study is that assessments were made without "blinding" the investigators or patients to the "on" and "off" digoxin periods. Although this study was not double-blinded or randomized, we believe the major findings are valid. Certain objective endpoints such as cardiothoracic ratio and radionuclide ejection fraction were interpreted blindly by the physicians without knowledge of which study was obtained on or off digoxin. Also, no increase in mean body weight was observed which might have indicated fluid retention. Another limitation might be the somewhat brief duration of follow-up off digoxin after which the second set of measurements was made. Nevertheless, after an average of 4 months of follow-up off digoxin, no evidence of clinical decompensation was observed.

In conclusion, we found that in most patients in sinus rhythm and documented CHF secondary to ischemic heart disease, digoxin can safely be discontinued when diuretic and vasodilator therapies are maximized. Only 2 of 24 patients in the present study showed an increase in heart failure score when digoxin was discontinued. In one of these patients, no clinical deterioration was observed >1 week after digoxin withdrawal. When diuretic therapy was also discontinued by the patient, signs of overt CHF promptly developed. No significant changes in left ventricular ejection fraction and cardiothoracic ratio at 1 month of digoxin discontinuance in the group as a whole were seen. The effects of digoxin withdrawal on regional wall motion were not assessed in the study. Although the global LVEF was unchanged after digoxin discontinuance, regional wall motion might have been altered. Similarly, despite no observed change in mean ejection fraction after digoxin discontinuance, certain patients may have experienced a decrease in cardiac output. The latter hemodynamic parameter was not obtained in this study. It must be emphasized again that in contrast to the majority of previous studies addressing the issues of efficacy of chronic digitalis therapy, all patients in the present study were digitalized initially for documented symptoms and signs of CHF. These data suggest that a randomized, double-blind study could safely be undertaken to assess the clinical use of digoxin therapy for heart failure in patients in sinus rhythm concurrently receiving diuretic or vasodilator drugs or both.

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Efficacy and Safety of Verapamil in Patients With Angina Pectoris After 1 Year of Continuous, High-Dose Therapy

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The long-term efficacy and safety of high-dose verapamil therapy (480 mg/day) was assessed in 26 patients with chronic stable angina pectoris during a 3-phase protocol: Phase 1—an initial, 6-week placebo-controlled, double-blind crossover assessment; Phase 2—an open label, 1-year follow-up; and Phase 3—a final drug withdrawal and rechallenge 10-week study. Three patients withdrew during Phase 2 (1 had hepatitis and 2 underwent coronary bypass surgery). Adverse effects during Phase 2 were mild, consisting of constipation (6 patients) and prolongation of the P-R interval (5 patients); however, no patient required alteration of the 480 mg/day dosage. At the end of Phase 2, 10 patients underwent the Phase 3 study, commencing with a 2-week period in which verapamil was either tapered gradually or abruptly discontinued. This was followed by an 8-week double-blind, placebo-controlled crossover rechallenge study with verapamil.

The clinical and exercise responses to verapamil compared with placebo were similar during the Phase 3 protocol and the initial Phase 1 study (treadmill time increased by 55% and anginal attacks per week decreased by 63% during Phase 3, compared with a 28% increase and a 42% decrease, respectively, during Phase 1, p = not significant [NS]). Withdrawal of verapamil produced a similar return of anginal symptoms whether the drug was abruptly discontinued or its administration tapered. No patient had unstable angina pectoris or acute myocardial infarction.

These investigations demonstrate that verapamil is safe and effective when evaluated after 1 year of continuous therapy using a dosage of 480 mg/day. There is no evidence of drug tachyphylaxis, nor does verapamil appear to cause an abrupt withdrawal syndrome in patients with chronic stable angina pectoris.

The development of calcium-channel blocking agents represents a tremendous advance in the treatment of ischemic heart disease. Verapamil belongs to this class of drugs, and its beneficial effects in the treatment of patients with exertional angina pectoris are well documented in several short-term controlled studies.[1–7] Its long-term efficacy and safety, however, have not been well demonstrated using a carefully designed trial.

We have previously reported that patients with stable exertional angina pectoris had a beneficial response to verapamil in a short-term controlled study.[8] The present investigation extends those initial observations to determine the efficacy and safety of high-dose verapamil therapy after 1 year of continuous therapy. Patients were then withdrawn from verapamil and rechallenged in a controlled trial for the following objectives: (1) to determine whether tachyphylaxis to the drug occurred after 1 year of therapy, and (2) to evaluate whether a withdrawal syndrome occurs upon abrupt cessation of verapamil therapy.

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Methods

Study population: Twenty-six male patients with a mean age of 55 years (range 30 to 72) were enrolled in the protocol. All patients were diagnosed as having chronic stable angina pectoris of at least 6 months in duration, having at least 5 episodes per week in addition to an abnormal treadmill exercise test, consisting of both ischemic (≥1 mm) S-T segment depression and exercise-induced angina. No patient had a history of congestive heart failure, systemic hypertension (>150/100 mm Hg), sinus bradycardia (<50 beats/min), atrioventricular block, renal or hepatic dysfunction, or myocardial infarction within the previous 3 months, although 10 patients had a history of myocardial infarction. Sixteen patients were classified as New York Heart Association func-

tional class 2 and 10 patients as functional class 3. Seventeen patients underwent coronary angiography: 4 had 1-vessel coronary disease, 6 had 2-vessel disease, and 7 had 3-vessel disease. Ninety-two percent of the catheterized patients had a left ventricular ejection fraction >50%. No patient had evidence of congestive heart failure on examination.

Study protocol (Fig. 1): The patients initially underwent a dose-seeking, single-blinded period. All patients tolerated verapamil in a dose of 480 mg/day without severe adverse effects. They then were enrolled in a protocol consisting of 3 separate phases. Phase 1 consisted of an initial 6-week, randomized, double-blind crossover study. The details of this phase have been reported elsewhere.[8] In brief, each patient received either placebo or verapamil, 480 mg/day, for 2-week periods, followed by a 1-week, drug tapering period. Phase 2 comprised a 1-year, open-label drug trial in which all patients received 480 mg/day of verapamil. No additional antianginal medication was administered during this phase except for sublingual nitroglycerin. Phase 3 consisted of a 10-week, randomized, placebo-controlled, double-blind crossover study after the patients were first withdrawn from verapamil. During the first 2 weeks of this phase, verapamil was discontinued either abruptly or tapered gradually over 4 days in a random fashion. The patients then entered an 8-week, randomized, double-blind crossover phase during which verapamil, 120 mg 4 times per day, or identical appearing placebo was administered for 2 weeks. At the end of the 2 weeks during which verapamil had been given (either crossover A or B), the drug was withdrawn either abruptly or tapered over 4 days, opposite to the method used during the initial 2 weeks. Thus, all the patients underwent both an abrupt withdrawal and a tapering (over 4 days) withdrawal from verapamil therapy. During Phase 3, as was done during Phase 1, the patients were permitted to use sublingual nitroglycerin as needed to treat anginal episodes, but no additional cardioactive medications were administered other than the test capsules, which were given 4 times daily.

The patients were evaluated weekly during Phase 1, every 3 months during Phase 2, and weekly during Phase 3 by the same research assistant and physician. Each patient signed an informed consent form approved by the Institutional Review Board at Boston University Medical Center at the beginning of each of the 3 phases of the protocol. If the patients did not wish to participate in Phase 3, they were continued indefinitely in the open-label trial.

Exercise tests: Treadmill exercise tests using the Bruce protocol[9] were performed 5 times during Phase 1, once at the end of Phase 2, and 5 times during Phase 3 (Fig. 1). A 12-lead electrocardiogram and blood pressure were recorded at rest and at 1-minute intervals during exercise and recovery, until the heart rate, blood pressure, and S-T segments returned to baseline. All patients were exercised maximally to a symptom-limited endpoint each time. Parameters analyzed on the exercise test included total exercise duration on the treadmill; time to the onset of 1 mm of horizontal or downsloping S-T segment depression; peak S-T segment depression; P-R interval at rest; and heart rate, systolic blood pressure, and rate-pressure product (heart rate × systolic blood pressure) at rest, during submaximal exercise (defined as the end of stage 1 of exercise), and maximal exercise.

Blood verapamil levels: Verapamil blood levels were sampled in each patient at the end of crossover A and B during Phase 1 and at the end of each 2-week period during Phase 3 (Fig. 1). Samples were drawn 2 hours after the last capsule had been ingested. Serum drug concentrations were measured at the Bioscience Laboratories, Chicago, Illinois, utilizing the high-pressure liquid chromatographic method of Harapat and Kates.[10] Verapamil blood levels were used to measure patient compliance in taking medication and to assess the completeness of drug washout.

Statistics: A 2-way analysis of variance for repeated measures was used to determine if significant differences occurred between the group mean values. If the analysis of variance indicated a significant difference in the mean values for a parameter, a 2-tailed, paired Student's t test was applied. Probabilities were considered significant at the 0.05 level. All values are expressed as mean ±1 standard deviation.

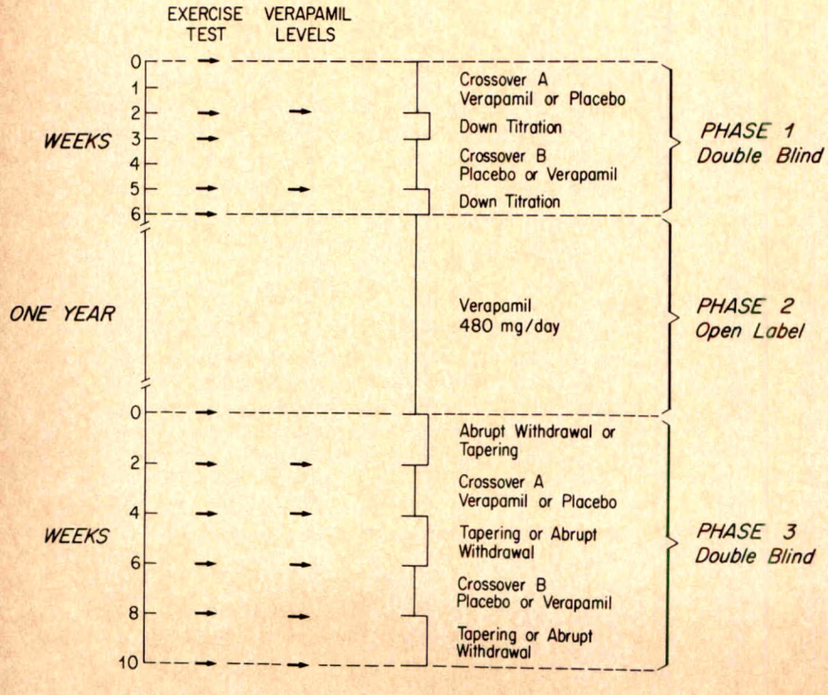

FIGURE 1. Protocol design. The entire protocol consisted of 3 phases: Phase 1, an initial 6-week, double-blind, crossover study; Phase 2, a 1-year, open-label, drug efficacy and safety trial; and Phase 3, a 10-week, double-blind, crossover drug withdrawal and rechallenge study.

TABLE I Acute and Long-Term Effects of Verapamil in 23 Patients

Variable	Phase 1: Placebo	Verapamil Therapy	
		Phase 1	Phase 2
Anginal episodes per week	6.3 ± 7.5	2.5 ± 4.1†	2.8 ± 5.1*
Nitroglycerin tablets per week	7.6 ± 10.2	2.7 ± 5.2*	3.0 ± 9.3*
Treadmill time (s)	372 ± 132	444 ± 108†	444 ± 156†
S-T segment depression			
Onset (s)	258 ± 114	336 ± 114†	366 ± 186†
Peak (mm)	2.4 ± 1.0	1.9 ± 1.0*	1.2 ± 0.8‡
Heart rate (beats/min)			
Rest	67 ± 11	61 ± 8*	64 ± 8
Submaximal exercise	102 ± 10	93 ± 8†	95 ± 10*
Maximal exercise	128 ± 15	124 ± 19	125 ± 16
Systolic blood pressure (mm Hg)			
Rest	125 ± 15	122 ± 16	123 ± 16
Submaximal exercise	144 ± 18	137 ± 15*	139 ± 22
Maximal exercise	163 ± 19	161 ± 21	157 ± 24
Rate-pressure product (beats/min·mm Hg × 10^{-2})			
Rest	84 ± 18	74 ± 13†	79 ± 13
Submaximal exercise	143 ± 25	127 ± 18†	132 ± 24
Maximal exercise	210 ± 38	201 ± 44	198 ± 44

Mean values ± 1 standard deviation.
* $p < 0.05$, compared with placebo.
† $p < 0.001$, compared with placebo.
‡ <0.05, Phase 2 versus Phase 1.

Results

Dropouts and drug safety: Twenty-six patients were entered into the protocol, and all completed Phase 1. One patient had abnormal liver function test results in Phase 1 at the end of crossover B while taking verapamil and was withdrawn from Phase 2. Two other patients dropped out during Phase 2 because of elective coronary bypass surgery at 5 and 10 months.

No patient required readjustment of the high-dose verapamil (480 mg/day) because of adverse effects during Phase 2. Minor adverse effects consisted of constipation in 6 patients (22%) approximately 1 week after starting verapamil, with 3 requiring treatment with stool softeners. Electrocardiographic changes were observed in 6 patients; five patients had prolongation of the P-R interval by 20 to 40 ms, but did not have first degree heart block, and 1 patient had intermittent, asymptomatic junctional rhythm at rest.

At the end of Phase 2, the remaining 23 patients were approached to undergo a 10-week drug withdrawal and rechallenge study (Phase 3) after they had been taking verapamil continuously for 1 year. Ten of the 23 patients were willing to participate in the Phase 3 study. These 10 patients did not differ from the 13 patients who refused to participate with respect to their clinical or exercise response to verapamil during Phase 1 or 2.

Long-term efficacy of verapamil (Phase 1 versus Phase 2): To determine the efficacy of verapamil over the 1 year follow-up, the clinical and exercise data of the 23 patients at the end of Phase 2 were compared with their initial results while taking placebo and verapamil, respectively, during Phase 1 (Table I). The improvement in the anginal attack rate, nitroglycerin consumed, and exercise duration while the patients were taking verapamil during Phase 1 continued to be demonstrated at the end of Phase 2.

The effects of verapamil on heart rate, blood pressure, and rate-pressure product were slightly different during Phase 1 and Phase 2. Heart rate at rest was significantly reduced compared with placebo during Phase 1, but not at the end of Phase 2. During submaximal exercise, heart rate, blood pressure, and rate-pressure product were significantly decreased with verapamil during Phase 1. At the end of Phase 2, however, only the heart rate during submaximal exercise differed from the placebo value. At maximum exercise, no differences were observed in heart rate, blood pressure, or rate-pressure product, while the patients were taking verapamil during either phase.

The effects of verapamil on the S-T segment response during exercise were similar during Phase 1 and at the end of Phase 2; both significant lengthening of the time

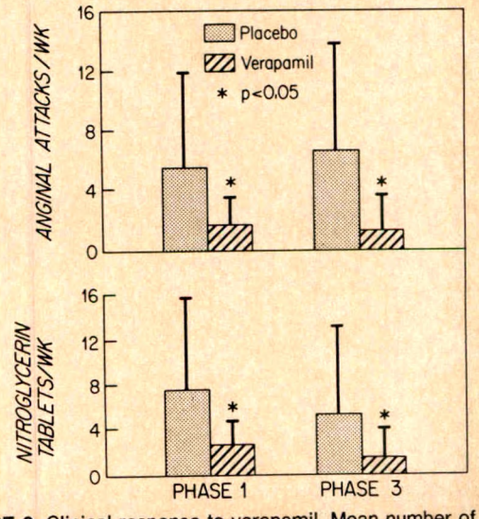

FIGURE 2. Clinical response to verapamil. Mean number of anginal attacks and nitroglycerin ingested per week in 10 patients during the initial study (Phase 1) **(left)** and during the follow-up study (phase 3) **(right)**.

TABLE II Clinical and Exercise Results Comparing the 2-Week Periods After Withdrawal of Verapamil (Abruptly or Tapering) and the Initial Placebo Period

Variable	Placebo	Withdrawal		p value
		Abrupt	Tapering	
Clinical				
Anginal attacks per week	6.6 ± 7.8	7.8 ± 8.5	7.6 ± 8.1	NS
Duration of angina (min)	. . .	2.2 ± 0.6	2.6 ± 1.2	NS
Nitroglycerin tablets per week	7.8 ± 8.5	6.3 ± 7.4	5.8 ± 9.6	NS
Exercise test				
Exercise duration (s)	362 ± 94	338 ± 171	296 ± 116	NS
Onset S-T depression (s)	258 ± 75	266 ± 135	252 ± 96	NS
Peak S-T depression (mm)	2.0 ± 0.8	1.6 ± 0.8	1.8 ± 1.0	NS
Rate-pressure product ($\times 10^{-2}$)				
Rest	100 ± 13	107 ± 11	106 ± 16	NS
Submaximal exercise	152 ± 26	159 ± 19	157 ± 25	NS
Maximal exercise	204 ± 44	207 ± 30	193 ± 30	NS

NS = not significant.

to the onset of S-T segment depression and reduction of the peak S-T segment depression were observed at each time period. The peak S-T segment depression was further reduced at the end of Phase 2 compared with the value with verapamil during Phase 1 (1.2 ± 0.8 versus 1.9 ± 1.0 mm, respectively, $p < 0.05$).

Rechallenge with verapamil (Phase 1 versus Phase 3): During the third phase of the protocol, 10 patients were withdrawn from verapamil after 1 year of therapy, and then rechallenged in an 8-week double-blind, crossover, randomized, placebo-controlled trial. The data from these 10 patients during their Phase 1 studies were compared with their results during Phase 3. The mean number of anginal episodes and nitroglycerin tablets consumed while taking verapamil was reduced by 42 ± 38 and 55 ± 42%, respectively, during Phase 1 ($p < 0.05$), and by 63 ± 46 and 75 ± 53%, respectively, during Phase 3 ($p < 0.05$) (Fig. 2). Exercise duration during verapamil therapy was increased by 98 ± 21 seconds during Phase 1 ($p < 0.001$) and by 140 ± 40 seconds during Phase 3 ($p < 0.01$) (Fig. 3). The beneficial effects of verapamil on these clinical and exercise variables were similar during Phase 3 and in Phase 1 (p = NS).

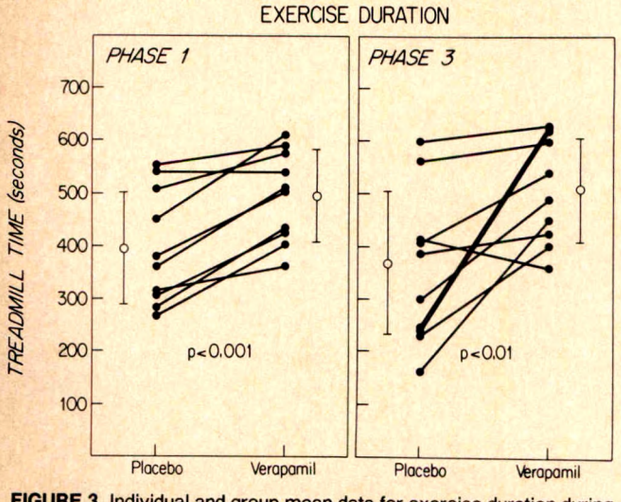

FIGURE 3. Individual and group mean data for exercise duration during the initial study (Phase 1) (**left**) and during the follow-up study (Phase 3) (**right**).

Abrupt withdrawal of verapamil (Table II): No patient had an unstable anginal syndrome or myocardial infarction during the 2-week period after the abrupt discontinuation of verapamil. There were no significant differences in either the number and duration of anginal attacks, the number of nitroglycerin tablets consumed, or the exercise response during the 2-week periods after abrupt cessation of verapamil compared with tapering of the drug. Moreover, there were no differences in the clinical and exercise responses when these 2 withdrawal periods were compared with the initial placebo period in the 10 patients.

Blood verapamil levels: Mean blood levels measured at the end of 2 weeks of verapamil therapy during Phase 1 were 298.1 ± 161.5 ng/ml (range 80 to 701) and during Phase 3 were 230.1 ± 119.3 ng/ml (range 61 to 467).

Discussion

Conventional drug therapy for the treatment of chronic stable angina has relied on the use of nitrate preparations[11,12] and beta-adrenergic blocking agents.[13,14] In some patients, however, intolerable adverse effects can occur.[15] Other patients have incomplete symptomatic relief even with combinations of these drugs. These considerations have led to a search for safe, alternative therapy for the treatment of angina pectoris.

The value of calcium-entry blocker drugs in treating patients with angina of effort has been demonstrated in numerous short-term, controlled trials.[1–8] The long-term efficacy and safety of verapamil in the treatment of angina pectoris, however, has not been well documented.

The present study shows that the benefits conferred by verapamil (480 mg/day) were maintained during a 1-year, open-label follow-up (Phase 2). Adverse effects from verapamil were minimal: constipation, remedied

by dietary adjustment or stool softeners and P-R interval prolongation on the resting electrocardiogram. None of these adverse effects required adjustment of the dosage of verapamil. Comparable beneficial actions of verapamil and paucity of adverse drug effects have been previously demonstrated when lower doses (360 mg/day) were given for 1 year.[16]

Verapamil achieved a similar reduction of anginal frequency and improvement in exercise tolerance during Phases 1 and 2. These beneficial effects have been attributed to a reduction in cardiac work,[4,8,16] mediated by a lower submaximal heart rate and rate-pressure product, findings corroborated in this study in both short-term (Phase 1) and long-term follow-up (Phase 2). Verapamil also caused a significant reduction of the peak S-T segment depression at a similar rate-pressure product, an effect which was greater at 1 year than at short-term follow-up. Less marked S-T segment depression at the same rate-pressure product may reflect enhancement of coronary perfusion to ischemic regions of myocardium.

The persistent beneficial effects of verapamil during Phase 2 at the end of 1 year in an open-label trial might have been due to spontaneous remission of angina pectoris, which has been observed to occur in up to one third of male patients,[17] rather than to the drug itself. To resolve this issue, a drug withdrawal and rechallenge study (Phase 3) was implemented 1 year after continuous verapamil therapy. Bala Subramanian et al[16] also performed a drug withdrawal study after 1 year of continuous verapamil therapy, in which exercise testing 4 weeks after reinstitution of placebo showed that there were no significant changes in the parameters analyzed compared with those on the initial placebo test. In contrast to the present study, the patients were not rechallenged with verapamil in a controlled protocol. The present investigation demonstrated that the patients had similar improvements in the symptomatic relief of angina pectoris and increased exercise duration when rechallenged with verapamil during Phase 3 as they had during the initial study in Phase 1. Thus, tachyphylaxis to verapamil did not occur, as has been suggested with nitrate therapy for the treatment of angina pectoris.[18,19] The persistent efficacy of verapamil appears due to the medication itself rather than to spontaneous disappearance of the anginal syndrome in the patients tested.

The beta-adrenergic blocking agents have been well documented as causing severe exacerbation of angina pectoris, myocardial infarction, and even sudden death when the drugs were abruptly discontinued.[20] This abrupt withdrawal syndrome may occur as late as 21 days after cessation of the medication.[21] Whether calcium-channel blocking agents may cause a similar exacerbation of ischemic events in patients with chronic stable angina is not known. One previous study did not note an exacerbation of anginal symptoms or myocardial infarction during a 1-week period when verapamil was withdrawn in 20 patients with chronic stable angina over a 3-day period.[22] In the present study, 10 patients were evaluated in a double-blind, crossover trial during both abrupt and gradual withdrawal from verapamil. None had unstable angina or myocardial infarction during abrupt cessation of verapamil. Moreover, anginal frequency and duration, nitroglycerin consumption, and exercise performance were similar during the 2-week evaluation periods after abrupt discontinuation of verapamil compared with its tapering (over 4 days), and when both withdrawal periods were compared with the initial placebo evaluation in the same patients.

The results of the present investigation demonstrate that verapamil is an effective and safe drug in the treatment of patients with stable angina pectoris. Sustained objective and subjective benefits from verapamil were seen for periods up to 1 year. Adverse effects from 480 mg/day of verapamil in this subpopulation of coronary patients were minimal. Abrupt withdrawal from verapamil was well tolerated and did not provoke unstable angina pectoris or myocardial infarction, as has been reported with beta-antagonist drugs.[20,21]

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Enhanced Detection of Proximal Right Coronary Artery Stenosis With the Additional Analysis of Right Ventricular Thallium-201 Uptake in Stress Scintigrams

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The value of right ventricular thallium-201 analysis in detecting proximal right coronary artery stenosis in exercise myocardial scintigraphy was analyzed in 52 patients, 27 with and 25 without proximal right coronary artery stenosis. For the detection of proximal right coronary artery stenosis, the sensitivity and specificity of thallium scintigraphic analysis were 59 and 88% for a right ventricular abnormality, 67 and 68% for a left ventricular inferior wall abnormality, and 93 and 56% for an abnormality of either. When both right and left ventricular thallium images were abnormal, all 9 patients had proximal right coronary artery stenoses, and when both were normal, 26 of 28 patients had a normal proximal right coronary artery. The sensitivity and specificity of blood pool scintigraphic variables during exercise (right ventricular ejection fraction and left ventricular inferior wall motion) were not significantly different for detection of proximal right coronary artery stenosis.

Thus, the additional analysis of the right ventricle on thallium-201 stress scintigrams can improve the detection of proximal right coronary artery stenosis. When both right ventricular and left ventricular thallium scintigrams are abnormal (or normal), the ability to predict the presence (or absence) of proximal right coronary artery stenosis is very high.

Visual analysis of left ventricular (LV) stress thallium-201 scintigrams has been extensively studied and found to be clinically useful in detecting coronary artery disease.[1–7] Nevertheless, LV scintigrams have an inherent limitation in localizing individual coronary artery stenoses, especially those of the right coronary artery (RCA) and left circumflex artery.[2,3,6,7] However, the right ventricle has not been included in the analysis of these thallium-201 images. Recent observations showed that although the right ventricle is not usually visualized at rest, it is seen after exercise as well as in conditions associated with right ventricular (RV) hypertrophy, and RV volume and pressure overload.[8–10] Right ventricular visualization has been related to an increase in RV myocardial blood flow.[11]

Subsequent to our initial observation[12] and the establishment of criteria[13] for RV thallium defects after stress in patients with coronary artery disease, this study was undertaken to evaluate the usefulness of RV thallium scintigraphic analysis in the detection of proximal RCA stenosis. In addition, we compared the ability of 2 blood pool scintigraphic variables, RV ejection fraction[14–17] and LV inferior wall motion,[18] during sequential 2-view exercise, to detect proximal RCA stenosis.

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Methods

Patient population: The study consisted of 52 patients with a history of chest pain who were referred to our cardiac stress laboratory because of suspected or known coronary artery disease. There were 43 men and 9 women with a mean age of 55 years (range 24 to 82). Of these, 11 had previous myocardial infarction, including 6 inferior and 5 anterior infarctions (Q wave ≥0.04 second), on electrocardiography. All patients underwent stress-redistribution thallium-201 myocardial scintigraphy, exercise blood pool scintigraphy, stress

electrocardiography, and cardiac fluoroscopy within 3 months of coronary arteriography.

Forty-six patients had coronary artery disease (defined as ≥50% reduction in diameter) on coronary angiography. Of these, 27 had triple-, 8 had double-, and 11 had single-vessel coronary artery disease (only 1 with isolated RCA stenosis). Six patients had normal coronary angiograms. Thirty-two patients had RCA stenosis, including 27 with stenosis proximal to the acute margin (Group I) and 5 with more distal stenosis (Group II). Twenty patients had either normal or <50% stenosis of the RCA (Group III). The sensitivity for the detection of proximal RCA stenosis was determined from Group 1 and the specificity from Groups II and III.

Exercise protocol: Thallium-201 scintigraphy was performed after treadmill exercise according to the Bruce protocol with continuous 12-lead electrocardiographic monitoring. Equilibrium blood pool scintigraphy was performed during upright bicycle exercise with a graded work load starting at 25 W and increasing every 3-minute stage by an additional 25 W. Imaging was performed in the last 2 minutes of exercise in each stage.

Exercise was maximal, terminated only for exhaustion or the development of severe angina, serious arrhythmia, or hypotension. At maximal exercise during treadmill thallium scintigraphy and during upright bicycle blood pool scintigraphy, heart rates (mean ± standard deviation) were 150 ± 26 and 148 ± 19 beats/min (p = not significant) and systolic blood pressures (mean ± standard deviation) were 171 ± 27 and 195 ± 26 mm Hg, respectively (p <0.001). All patients on beta-blocking drugs were asked to withold this medication for 24 to 48 hours before exercise testing.

Thallium-201 scintigraphy: A dose of 2 mCi of thallium-201 was injected intravenously at near maximal treadmill exercise, and exercise was continued an additional 45 to 60 seconds. Serial, multiple-view myocardial scintigrams were obtained, beginning approximately 6 minutes (immediate poststress imaging) and 3 to 5 hours (redistribution imaging) after the injection of thallium. For each phase of imaging, 10-minute images were obtained in the anterior and 45° and 70° left anterior oblique projections. Imaging was performed using a standard field-of-view Anger camera equipped with 37 photomultiplier tubes, an 0.25 inch thick sodium iodide crystal, and a high-resolution parallel-hole collimator. A 25% energy window centered on the 80 keV X-ray peak and another independent 15% window centered on the 167 keV photopeak were used. All scintigrams were recorded on Polaroid film with a triple-lens camera.

The thallium images from each patient were examined jointly by 2 experienced observers without knowledge of the clinical history or results of coronary angiography. For both the poststress and 4-hour redistribution scintigrams, the inferior wall of the left ventricle in each of the anterior and 70° left anterior oblique views and the right ventricle in the 45° left anterior oblique view were divided into 2 segments. Thallium activity was visually assessed for each region by a 4-point scoring system: 0 = normal, 1 = slightly decreased but almost normal, 2 = definitely decreased, and 3 = severely decreased. Differences in scores were mediated by consensus. For the left ventricle a perfusion defect was defined by a segmental score of at least 2. For the right ventricle a perfusion defect was considered present if a comparative difference in thallium-201 uptake of at least 1 score occurred between the 2 segments or if a marked diminution or absence of thallium-201 uptake occurred in both segments. Because of the differences in muscle mass and regional blood flow between the right and left ventricle, the left ventricle was not used as an absolute guide when assessing RV thallium uptake. Thus, small relative differences in thallium activity between the right and left ventricle were considered normal.

Blood pool scintigraphy: Multiple-gated equilibrium blood pool scintigraphy was performed as follows: after the intravenous injection of 25 mCi of in vitro labeled autologous technetium-99m red blood cells, data were acquired with a portable scintillation camera (Picker) equipped with a parallel-hole, low-energy, all purpose collimator and a dedicated minicomputer (A^2 Medical Data Systems). During each 2-minute acquisition period, the computer divided the scintigraphic data from each cardiac cycle into 20 frames. An average of 100,000 counts per frame was collected using a 25% energy window centered on the 140 keV photopeak of technetium-99m. Exercise imaging was first performed in the 40° to 50° left anterior oblique view and, after a 20- to 30-minute rest period, was repeated in the anterior view.[19] For the anterior view, a 5° to 10° caudal tilt was employed if it provided a better separation of the right and left ventricles. During exercise, a foam wedge was inserted into the space between the obliquely angulated scintillation camera and the patient, and the patient was then strapped to the scintillation camera to minimize patient motion.

The determination of RV ejection fraction involved light pen assignment of 2 regions of interest over the right ventricle in the left anterior oblique view, 1 in end-systole and the other in end-diastole, and then dividing the stroke counts (end-diastolic counts − end-systolic counts) by background-corrected end-diastolic counts.[14]

Left ventricular inferior wall motion was assessed in the anterior view using a 5-point scoring system (−1 = dyskinesia, 0 = akinesia, 1 = severe hypokinesia, 2 = mild hypokinesia, and 3 = normal).[20]

The right ventricular ejection fraction response to exercise was considered normal if the exercise ejection fraction increased by at least an absolute 5% from the resting value. Left ventricular inferior wall motion was analyzed by the consensus of 2 experienced observers unaware of any clinical informa-

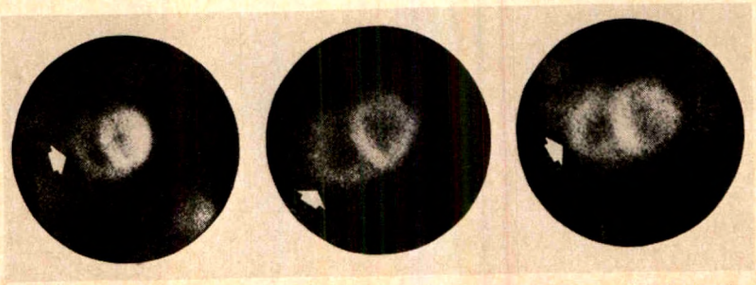

FIGURE 1. Normal right ventricular stress thallium scintigrams (**arrows**) in the 45° left anterior oblique view in 3 patients with a normal right coronary artery.

tion, and was considered abnormal when the wall motion score at maximal exercise was <3. Inferior segments obscured by RV overlap were excluded from analysis.

Assignment of RCA territory to scintigraphic images: Both segments of the RV image on the thalllium-201 scintigrams and the right ventricle on the blood pool scintigrams were considered to represent the distribution of the proximal RCA. The LV inferior wall of the thallium-201 scintigrams (anterior and 70° left anterior oblique views) and the inferior wall of the blood pool scintigrams (anterior view) were considered to represent the distribution of either the proximal or the distal RCA.

Coronary arteriography: Selective coronary arteriography was performed in multiple views using the Judkins technique. The RCA was divided into 2 segments, 1 proximal and the other distal to the acute margin of the heart. Each coronary angiogram was graded by 2 observers who were unaware of the results of noninvasive testing. Significant stenosis was considered present when there was ≥50% diameter narrowing of the RCA. Of the 52 patients who had coronary angiography, 10 patients had a nondominant RCA; 6 had left dominant systems and 4 had balanced systems. Both the RCA and left circumflex coronary artery had significant stenoses in 4 of the 10 patients, and both the RCA and left circumflex coronary artery were normal or had insignificant stenoses in 6 patients.

Statistical analysis: McNemar's test was used to assess the significance of the difference in sensitivity and specificity between RV and LV scintigraphic analysis in the detection of proximal RCA stenosis.[21] Whenever the expected cell frequencies were <5, the binomial test was used. A p value <0.05 was considered significant.

Results

Sensitivity and specificity of thallium-201 scintigraphy: Sixteen of 27 Group I patients were considered abnormal by visual assessment of RV thallium-201 images (sensitivity 59%). Right ventricular thallium-201 scintigrams showed nothing abnormal in all 5 patients in Group II and in 17 of 20 in Group III (specificity 88%).

For detection of a proximal RCA stenosis, LV thallium-201 scintigraphy resulted in a sensitivity of 67% (18 of 27 in Group I were considered abnormal) and a specificity of 68% (2 of 5 in Group II and 15 of 20 in Group III). These results were not significantly different from those on RV analysis. When either RV or LV thallium-201 scintigraphic techniques were abnormal, 25 of 27 patients (93%) in Group I were detected (p <0.01 compared with RV or LV thallium-201 images analyzed separately). The specificity of the combined analysis was 14 of 25 or 56% (p <0.05).

When only concordant RV and LV scintigrams were analyzed, all 9 patients who had both abnormal RV and LV thallium-201 images had proximal RCA stenosis. Conversely, of 28 patients with both normal RV and LV scintigrams, 26 had a normal proximal RCA. Of the 6 patients with inferior myocardial infarction, 3 had abnormal RV and 6 had abnormal LV thallium scintigrams. Representative LV and RV thallium scintigrams of patients with and without a proximal RCA stenosis are illustrated in Figures 1 to 4.

Comparison of blood pool scintigraphic variables: Fifteen of 27 Group I patients had an abnormal RV ejection fraction response to exercise (sensitivity 56%), whereas 4 of 5 patients in Group II and 12 of 20 in Group III had a normal response (specificity 64%). For detection of a proximal RCA stenosis, analysis of the LV inferior wall at peak exercise resulted in a sensitivity of 59% (16 of 27 Group I patients) and a specificity of 64% (3 of 5 Group II and 13 of 20 Group III patients). Neither the sensitivity nor the specificity of RV ejection fraction or inferior wall motion differed significantly from RV thallium analysis for the detection of proximal RCA stenosis.

When both RV ejection fraction and LV inferior wall motion were analyzed, the sensitivity was 81% (22 of 27 Group I patients) (p <0.05) and the specificity 48% (3 of 5 Group II and 9 of 20 Group III patients) (p <0.05). Of 14 patients with abnormal RV ejection fraction and LV inferior wall motion, only 9 had proximal RCA stenosis, and of 28 patients with both normal RV ejection fraction and LV inferior wall motion, 23 had a normal proximal RCA. Two of 6 patients with inferior myocardial infarction had abnormal RV ejection fractions, and 6 of 6 had abnormal LV inferior wall motion.

Discussion

Detection of proximal RCA stenosis: The results of the present study demonstrate that the addition of analysis of the RV to the inferior LV wall of stress thallium-201 images improves sensitivity in the detec-

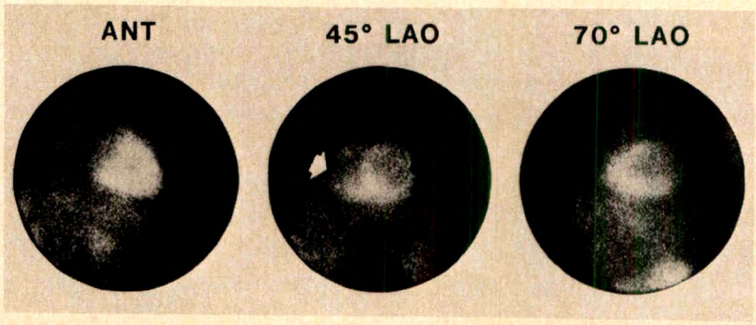

FIGURE 2. Proximal defect (**arrow**) in the right ventricular stress thallium scintigram in the 45° left anterior oblique view (LAO) of a patient with a proximal right coronary artery (RCA) stenosis. Of note, the inferior wall of the left ventricle in both the anterior (ANT) and 70° left anterior oblique view has normal thallium uptake. This is an example of a proximal RCA stenosis detected by right but not left ventricular inferior wall analysis.

tion of proximal RCA stenosis. Although the sensitivity of RV and LV thallium scintigrams was not significantly different, their combined analysis did improve the ability to detect proximal RCA stenosis, with a decrease in specificity. For exercise blood pool scintigraphy, the sensitivity for the detection of proximal RCA stenosis also improved when the analysis of RV ejection fraction and LV inferior wall motion was combined.

Until recently the interpretation of stress thallium scintigrams has been limited to the left ventricle for the detection of RCA stenosis. In previous studies, the results that were obtained (sensitivity between 50% and 73%) are similar to those of our study when analysis of the left ventricle only was performed.[2,3,6,7,22] Two other recent reports have also described the use of RV thallium-201 scintigrams to detect proximal RCA stenosis. The first of these was performed at rest during vasodilation with dipyridamole.[23] In this study, the sensitivity and specificity were similar to those we described, again with improvement in sensitivity from 60% when the left ventricle was analyzed to 93% when the RV was also assessed. However, the other experiment, performed with exercise, showed only a small nonsignificant change in sensitivity from 67% for LV inferior wall imaging to 78% for both RV and LV scintigrams.[24]

Of potential clinical importance is the predictive ability of the concordant interpretation of both RV and LV scintigrams. When the thallium images of the right and left ventricle were normal, the proximal RCA was normal in 93% of patients and, conversely, when both scintigrams were abnormal, there was a proximal stenosis in 100% of cases. These results of concordant thallium-201 scintigraphic interpretations again agree with the results of RV and LV imaging after dipyridamole when the combination of normal RV and LV inferior wall distribution of thallium was highly predictive for the absence of a proximal RCA stenosis.[23] In the exercise thallium-201 study abstracted by Brown et al,[24] 75% of patients with both normal RV and LV images had neither a proximal nor a distal RCA stenosis. This percentage is lower than ours and may be due to the inclusion of distal RCA stenosis in their analysis.

In contrast to thallium analysis, concordant results of blood pool scintigraphy were not as accurate. When both RV ejection fraction and LV inferior wall motion were normal, the proximal RCA was normal in 82%. However, when both were abnormal, proximal RCA stenosis was found in only 64%.

Perhaps the most important limitation in the assessment of thallium uptake in the RV free wall is that common to the visual analysis of LV thallium scintigrams, that is, the subjective variation in the interpretation of defects.[22] In the future, quantitation of the initial distribution and washout of thallium-201,[25] if applied to the right as it has been to the left ventricle, may decrease the subjectivity of this analysis.

Clinical implications: Our study indicates that the previously reported suboptimal sensitivity for the de-

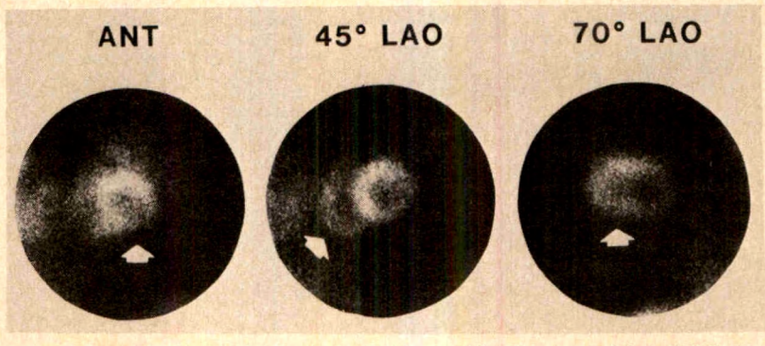

FIGURE 3. Left ventricular inferior wall stress defects in the anterior (ANT) and 70° left anterior oblique (LAO) views (**arrows**) in a patient with a proximal right coronary artery stenosis. Normal right ventricular thallium uptake in the 45° LAO view (**arrow**) is noted.

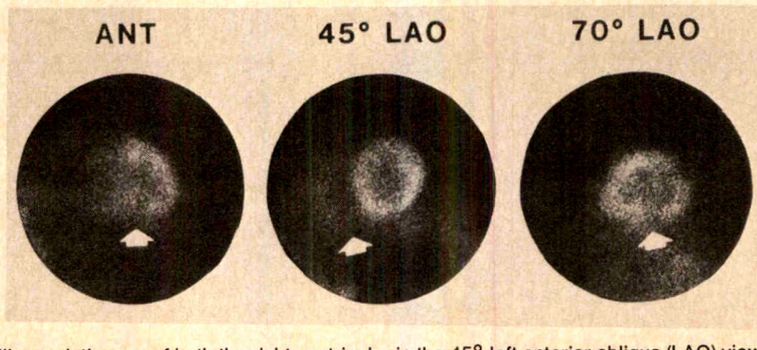

FIGURE 4. Defects in the thallium scintigrams of both the right ventricular in the 45° left anterior oblique (LAO) view (**arrow**) and the inferior wall of the left ventricle in the anterior (ANT) and 70° LAO views (**arrows**) of a patient with a proximal right coronary artery stenosis. This pattern is highly predictive of a proximal right coronary artery stenosis.

tection of individual coronary artery stenoses with the visual analysis of stress thallium scintigrams can be improved to detect proximal RCA stenosis by the additional interpretation of RV thallium uptake. The assessment of RV thallium uptake may improve the ability to detect patients with multivessel coronary disease using stress thallium-201 scintigraphy, which is limited by the low sensitivity for detecting RCA and left circumflex coronary stenoses.[6]

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Prognostic and Predictive Value of Exertional Hypotension In Suspected Coronary Heart Disease

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HAROLD T. DODGE, MD, and MAY ZIA, MS

The prognostic and predictive value of exertional hypotension was assessed in 1,241 patients having treadmill maximal exercise testing, coronary arteriography, and follow-up averaging 5.4 years. Medically treated patients with coronary artery disease (CAD) with exertional hypotension had poorer survival than did those without such hypotension; however, maximum systolic pressure during exercise was a more powerful predictor of survival. Patients with exertional hypotension had more extensive CAD and more left ventricular (LV) dysfunction than did patients who had an increase in blood pressure with exertion; these findings probably account for the impaired survival. However, exertional hypotension, was an insensitive indicator of significant left main coronary artery stenosis, 3-vessel disease, or severe resting LV dysfunction.

The normal response to upright dynamic exercise such as walking or running is an increase in systolic pressure as measured by a cuff at the arm.[1,2] Exertional hypotension, defined here as a decrease in exercise systolic pressure below resting systolic pressure, is commonly considered an ominous finding and an indication for invasive evaluation. Previous studies have shown a strong association of exertional hypotension with multivessel coronary artery disease (CAD)[3,4] and a likelihood of the development of ventricular fibrillation if exercise is continued.[5] However, the late prognostic significance of exertional hypotension in relation to other commonly used noninvasive and invasive prognostic indicators has not been reported. This study assesses the prognostic value of this variable both univariately and multivariately in a population of patients with suspected CAD. The sensitivity and predictive power of exertional hypotension in detecting critical CAD and resting left ventricular (LV) dysfunction in a large coronary arteriography registry are also reported.

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Methods

The characteristics of the Seattle Heart Watch Angiography Registry have previously been described in detail.[6,7] Briefly, all 5 hospitals in Seattle in which coronary arteriography is being performed agreed to enter patients undergoing this procedure for suspected CAD into a prospectively followed registry with the primary goal of identifying patients at risk for sudden cardiac death. Between 1969 and 1974 inclusively, 733 initially medically treated patients and 1,881 surgically treated patients were entered into this registry.

The extensive baseline characterization of these patients included data items from the history, physical examination, resting electrocardiogram, chest film, maximal treadmill exercise test (Bruce protocol[8]), coronary arteriogram, and quantitative angiographic assessment of LV function. Patients were exercised to symptom-limited maximum, although a decrease in systolic blood pressure during submaximal exercise was commonly used as an indication for physician termination of testing. Blood pressure was measured near the end of each 3-minute stage of exercise by arm cuff. The only significant complication of exercise testing in this series occurred in a single patient who required cardioversion for ventricular tachycardia.

The decision in regard to medical versus surgical therapy was made by the patient's physician or physicians on the basis of clinical findings and the results of the coronary arteriogram. Follow-up in regard to death and nonfatal cardiovascular endpoints occurred at 6-month intervals by mailed questionnaire; mean follow-up was 5.4 years with maximum follow-up >10 years.

The initial portion of this report giving baseline characteristics and survival analyses of patients with and without exertional hypotension is restricted to the 557 initially med-

TABLE I Comparison of Baseline Characteristics of Medically Treated Coronary Artery Disease Patients With and Without Exertional Hypotension: Discrete Variables

Variable	No Exertional Hypotension			Exertional Hypotension			p
	n	Total	%	n	Total	%	
Male sex	421	522	81	33	35	94	<0.05
Angina	397	517	77	32	35	91	<0.05
Unstable angina	203	522	39	21	35	60	<0.05
Congestive heart failure	41	516	8	6	34	18	<0.05
Functional class III, IV	147	505	29	17	34	50	<0.05
Digitalis use	67	522	13	9	34	26	<0.05
Diuretic use	93	521	18	11	34	32	<0.05
Propranolol use	86	510	17	8	34	24	NS
Previous myocardial infarction	190	522	36	21	35	60	<0.01
S_3 gallop	28	515	5	6	34	18	<0.01
Cardiomegaly	45	515	9	1	34	3	NS
Exertional S-T depression ≥1 mm	261	522	50	19	35	54	NS
Collateral vessels	209	482	43	23	31	74	<0.01
Left main stenosis (≥50%)	17	519	3	2	35	6	NS
Mitral regurgitation	11	487	2	7	28	25	<0.01
Left ventricular angiogram (dyskinesia or hypokinesia)	48	510	9	12	32	38	<0.01
Vessels (n) with stenosis ≥70%							
0	221	522	42	3	35	9	<0.001
1	151	522	29	12	35	34	
2	100	522	19	11	35	31	
3	50	522	10	9	35	26	

NS = not significant.

ically treated patients who had maximal treadmill exercise testing at the time of entry into this registry. For analyses of baseline characteristics predictive of exertional hypotension and sensitivity, specificity, and risk ratios of exertional hypotension in detecting critical coronary stenoses or severe LV dysfunction, data in all 1,241 patients (medically and surgically treated) with exercise testing were used.

Comparison of baseline characteristics between patients with and those without exertional hypotension was performed using the chi-square test for discrete variables and Student's *t* test for continuous variables. A stepwise logistic regression analysis was used to identify patients in whom exertional hypotension was likely to develop and specifically to test the effect of propranolol on the development of exertional hypotension. The survival of patients with and those without exertional hypotension was calculated by the life-table technique,[9] with differences in survival tested by the Mantel-Haenszel-Cox statistic.[10] The hypothesis that exertional hypotension is an independent predictor of survival after adjusting for other baseline characteristics was tested using Cox's regression analysis which assumes a proportional hazards model.[11] Sensitivity, specificity, and risk ratio were calculated as follows, where TP = true positives, FP = false positives, TN = true negatives, and FN = false negatives: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); risk ratio = [TP/(TP + FP)] × [(FN + TN)/FN].

Results

Characteristics of patients with exertional hypotension: Tables I and II compare the baseline characteristics between the 35 medically treated patients with and the 522 without exertional hypotension. In general, patients with exertional hypotension were more symptomatic, had poorer exercise performance, had more CAD, and poorer LV function. The frequency of propranolol use was not significantly different between patients with exertional hypotension (24%) and those without it (17%). The mean decrease in systolic pressure from resting to submaximal or maximal exercise was 19 mm Hg in the exertional hypotension subgroup compared with a 41 mm Hg increase in the subgroup without exertional hypotension.

Prognostic value of exertional hypotension: Figure 1 compares the actuarial survival of medically treated patients with and without exertional hypotension. The 5-year survival probability for patients with exertional hypotension is 0.71 ± 0.08, but is 0.88 ± 0.02 for patients without exertional hypotension. The difference between the 2 curves is highly significant (chi-square = 8.529; p <0.001).

The prognostic value of exertional hypotension and maximum systolic pressure during exercise in relation to other noninvasive variables was studied using Cox's regression analysis (Table III). Noninvasive variables significantly predictive of survival of medically treated patients in order of their level of significance are: a history of congestive heart failure, cardiac enlargement detected on chest film, maximum systolic pressure during exercise, S-T segment depression on resting electrocardiogram, age, and any ventricular arrhythmia on the resting electrocardiogram. When adjusted for the simultaneous prognostic effect of maximum systolic pressure and these other variables, exertional hypotension is not predictive of survival. We also tested the prognostic significance of exertional hypotension, adjusting only for the 2 most powerful predictors from the history: congestive heart failure and age. Using the Cox model, exertional hypotension is not significantly predictive of survival (p = 0.075) when adjusting only for these 2 variables.

Characteristics predictive of exertional hypotension: To identify variables independently predictive of the development of exertional hypotension, the statistically significant variables in Tables I and II (exercise variables were excluded)

TABLE II Comparison of Baseline Characteristics of Medically Treated Coronary Artery Disease Patients With and Without Exertional Hypotension: Continuous Variables

Variable	No Exertional Hypotension		Exertional Hypotension		
	n	Mean ± SD	n	Mean ± SD	p
Age (yr)	522	50 ± 8	35	54 ± 8	0.06
Diastolic blood pressure (mm Hg)	511	82 ± 10	34	72 ± 12	NS
Exercise duration (seconds)	515	357 ± 153	35	272 ± 146	<0.01
Functional aerobic impairment (%)	522	33 ± 23	34	43 ± 24	<0.05
Change in systolic pressure during exercise (mm Hg)	498	41 ± 21	35	−19 ± 20	<0.01
Maximum heart rate (ETT) (beats/min)	520	150 ± 24	35	139 ± 26	<0.01
Maximum systolic pressure (ETT) (mm Hg)	498	167 ± 27	34	120 ± 24	NS
Maximum pressure rate Product × 1,000 (ETT)	497	252 ± 65	35	166 ± 46	<0.01
LV end-diastolic pressure (mm Hg)	461	12.5 ± 11.0	29	16.2 ± 15.5	NS
End-diastolic volume (ml/m^2)	421	74.8 ± 27.2	27	81.0 ± 28.9	NS
End-systolic volume (ml/m^2)	421	32.8 ± 25.8	27	42.9 ± 27.1	<0.05
Ejection fraction	453	59.0 ± 15.7	28	50.9 ± 15.6	<0.01

ETT = exercise tolerance test; n = number of patients in whom variable was measured; p = significance of difference between means; SD = 1 standard deviation.

plus propranolol use were entered into univariate and multiple logistic analyses. The results are shown in Table IV. Although propranolol use was not univariately associated with exertional hypotension (neither in the chi-square analysis nor in the univariate logistic model), it and LV contraction grade were the only 2 variables significantly associated with exertional hypotension in the multivariate model.

Predictive value of exertional hypotension: The relation between exertional hypotension and left main coronary artery stenosis ≥50% diameter reduction, 3-vessel disease (stenoses ≥70%), and severe resting LV dysfunction (ejection fraction ≤30%) is shown in Table V. Although left main coronary disease and 3-vessel disease are significantly more frequent in patients with exertional hypotension, the use of this variable alone detected only a minority of patients with these coronary lesions. The proportion of patients exhibiting exertional hypotension who have ejection fractions ≤30% (5 of 81, 6%) is not significantly different from the proportion of

TABLE III Prognostic Value of Exertional Hypotension in Relation to Other Noninvasive Variables Tested With Cox's Regression Analysis (n = 497)

Variable	p
Congestive heart failure	0.0003
Cardiomegaly	0.0029
Maximum systolic blood pressure (ETT)	0.0032
S-T segment depression (resting ECG)	0.0223
Age	0.0227
Ventricular arrhythmia (resting ECG)	0.0475
S_3 gallop	0.0525
Functional class	0.4101
Exertional hypotension (ETT)	0.4615

ECG = electrocardiogram; ETT = exercise tolerance testing; N = number of medically treated patients in whom all variables were known; p = statistical significance of variable in predicting survival (death) while adjusting for the other variables.

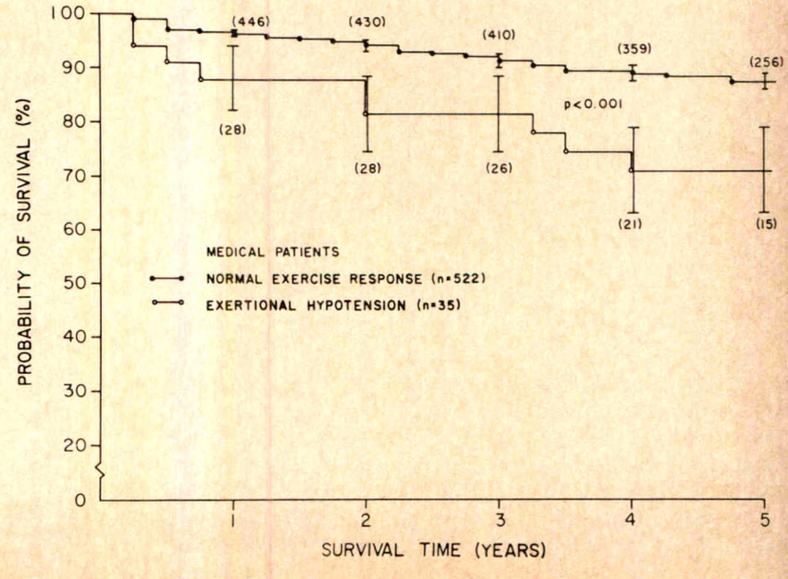

FIGURE 1. Actuarial survival curve of medically treated patients with and without exertional hypotension.

TABLE IV Stepwise Logistic Analysis to Identify Variables Independently Associated With the Development of Exertional Hypotension and Specifically to Test the Effect of Propranolol Use on the Development of Exertional Hypotension

Variable	Univariate Chi-Square	Multivariate Chi-Square
Left ventricular contraction grade	13.8*	5.6*
Number of vessels with stenosis ≥50%	11.0*	0.3
Collateral vessels present	8.4*	0.8
Functional class	4.8*	1.3
Ejection fraction	4.4*	0.8
Sex	4.2*	1.4
Propranolol use	. . .	4.9*

* $p < 0.05$.
N = 787 (65 with exertional hypotension).

patients without exertional hypotension who have low ejection fractions (37 of 937, 4%).

For the detection of patients with left main coronary artery stenosis ≥50%, exertional hypotension has a sensitivity of 15% (15 of 101), a specificity of 93% (1,051 of 1,127), and a risk ratio of 2.18 to 1. Similarly, for the detection of patients with 3-vessel disease (stenoses ≥70%), exertional hypotension has a sensitivity of 15% (42 of 271), a specificity of 95% (919 or 970), and a risk ratio of 2.26:1. Finally, for the detection of severe left ventricular dysfunction (ejection fraction ≤30%), the findings are similar: sensitivity 12% (5 of 42), specificity 92% (900 of 976), and risk ratio 1.56 to 1. The high specificities are a reflection of the relatively low prevalence rates of left main coronary artery stenosis, 3-vessel disease, and severe left ventricular dysfunction in the total population. These data should not be interpreted to mean that the absence of exertional hypotension gives any reliability of the absence of these 3 conditions.

Discussion

Exertional hypotension, which was prevalent in the Seattle Heart Watch Angiography Registry in 7.5% (93 of 1,241) of patients having exercise tests, is associated with more severe symptoms, more advanced CAD, and greater LV dysfunction. In a multivariate logistic analysis LV contraction grade and propranolol use were the only 2 variables significantly associated with the development of exertional hypotension. When examined alone, exertional hypotension is an indicator of impaired prognosis; however, when tested in the multivariate Cox model, the correlated variable, maximum systolic pressure with exertion, is a better predictor of survival. Exertional hypotension is an insensitive technique to identify patients with critical CAD or severe resting LV dysfunction.

The prevalence of exertional hypotension depends on the nature of the population being studied and the methods of exercise testing, including criteria for termination of exercise. Morris et al[4] reported no occurrence of exertional hypotension in 560 clinically normal male subjects and in only 1 of 159 patients with chest pain syndrome and normal coronary arteriograms. The latter findings are similar to data from our Seattle Heart Watch Arteriography Registry in that only 3 of 221

TABLE V Relation of Exertional Hypotension to Left Main Coronary Stenosis (≥50%), 3-Vessel Disease (Stenoses ≥70%), or Severe Left Ventricular Dysfunction (Ejection Fraction ≤30%) in Medically and Surgically Treated Patients With Coronary Arteriography

	Exertional Hypotension				
	Absent		Present		
	n	%	n	%	p
Left main stenosis					
<50%	1,051	92	76	84	
>50%	86	8	15	16	0.003
Total	1,137	100	91	100	
Three-vessel disease					
Absent	919	83	51	61	
Present	183	17	32	39	0.001
Total	1,102	100	83	100	
Ejection fraction					
>30%	900	96	76	94	
≤30%	37	4	5	6	0.128
Total	937	100	81	100	

p = significance of difference in distribution from chi-square analysis.

TABLE VI Comparison of Reported Frequency of Left Main Coronary Stenosis and 3-Vessel Disease Among Patients with Exertional Hypotension

	Three-Vessel Disease		Left Main Stenosis	
Author	N/T	%	N/T	%
Thomsen and Kelemen[3]	11/15	73	5/15	33
Morris et al[4]	15/22	68	3/22	14
Levites et al[12]	4/25	16	1/25	4
Li et al[13]	27/37	73	13/37	35
Weiner et al[18]	19/47	40	7/47	15
Hammermeister	42/93	45	15/91	16
Total	118/239	49	44/237	19

N = number of patients with 3-vessel disease or left main stenosis; T = total number of patients with exertional hypotension undergoing coronary arteriography.

patients (1.4%) with suspected CAD but normal coronary arteriograms (no stenosis ≥70%) had exertional hypotension. Irving et al[14] document a progressively decreasing maximum systolic pressure on exertion with increasing extent of CAD. Anderson et al[15] report an abnormal exercise blood pressure response (exertional hypotension in 6; decreasing systolic pressure in 10) in 16 of 25 patients with left main coronary artery stenosis ≥50%. Among our medically treated patients the prevalence of exertional hypotension increased from 7.4% (12 of 163) in patients with single-vessel disease to 10% (11 of 111) in patients with 2-vessel disease and to 18% (9 of 50) in patients with 3-vessel disease. Although the likelihood of having exertional hypotension clearly increases with increasing extent of coronary disease, the reported prevalence in patients with 3-vessel disease ranges from 16 to 73%, and from 4 to 35% in patients with left main coronary artery stenosis (Table VI). Despite the wide range of prevalence, the likelihood of

3-vessel disease or left main coronary stenosis in patients with exertional hypotension is sufficiently high (50%; 47 of 93 in the present series) to warrant careful attention. If other obvious causes of exertional hypotension are not present (obstructing valve lesions, obstructive cardiomyopathy, hypotension occurring at very high work loads, or propranolol use, as subsequently described), coronary arteriography probably should be performed, particularly because patients with these coronary artery lesions have prolonged survival with surgical therapy.[16,17]

Exertional hypotension, however, cannot be relied on to detect patients with 3-vessel disease or significant left main stenosis as the sensitivity is very low (15%). Most (85%) patients with these critical lesions will not exhibit exertional hypotension. Weiner et al[18] report low sensitivities very similar to ours in the detection of patients with left main coronary artery stenosis (21%) and 3-vessel disease (24%). The data of Irving et al[14] suggest that the requirement of a decrease in exercise blood pressure below the resting level is too stringent a test for the detection of 3-vessel disease. Their 180 patients with 3-vessel disease had an average increase in systolic pressure during exercise of about 20 mm Hg, even though this increment was less than half that in the 85 patients without significant CAD on arteriography. Dell' Arciprete et al[19] report that 60% of patients with multivessel disease (including 9 of 10 with significant left main coronary artery stenosis) had a maximum increase in systolic pressure with bicycle exercise ≤40 mm Hg. Using a less strict definition of abnormal exertional blood pressure response (failure to increase 10 mm Hg or more or an initial increase and then a decrease ≥20 mm Hg), Sanmarco et al[20] report a higher sensitivity of 39% in the detection of 3-vessel or left main CAD. Specificity was still high at 87%. Thus, the use of a subnormal increment in systolic pressure with exertion is a clinically more useful tool to select patients at high risk for left main CAD or 3-vessel disease than is exertional hypotension.

Left ventricular dysfunction as measured by the contraction grade is more strongly associated with exertional hypotension than with the extent of CAD, as the latter variable drops out in the multivariate logistic analysis. Although contraction grade and ejection fraction are highly correlated, the former, based on a subjective assessment of LV contraction patterns, seems to be a better predictor of exertional hypotension. We have used the scale of I to V described by Hamilton et al[21] in which I is normal and V is generalized hypokinesia or akinesia involving ≥75% of the ventricular circumference.

Even though propranolol is not univariately associated with exertional hypotension, the multivariate logistic model documents a significant relation between propranolol use and the development of exertional hypotension when simultaneous adjustment is made for LV function and the other variables in Table III. Exertional hypotension developing in patients taking propranolol may be the result of the drug and not necessarily of more extensive disease. We would not recommend that the development of exertional hypotension in patients on full doses of propranolol be used as the sole indication for invasive studies.

As shown in Figure 1, exertional hypotension is an indicator of impaired prognosis in this population of nonoperated patients having both exercise testing and coronary arteriography and including patients with and without significant CAD. In another analysis confined to nonoperated patients with significant CAD (stenoses ≥50%), exertional hypotension was not significantly predictive of survival.[22] Exertional hypotension appears to be a more powerful predictor of prognosis in populations in which the presence or absence of CAD is unknown, than in populations with proven CAD. This fact is presumably due to the uncommon occurrence of exertional hypotension in patients without CAD (other types of heart disease excluded) and the good prognosis of these patients.

In our multivariate analyses, maximum systolic pressure with exertion was a more powerful predictor of survival than exertional hypotension, as has been previously reported by Irving et al[14] and Bruce et al.[23] In our analyses confined to nonoperated patients with significant CAD, the maximum pressure-rate product was a significant predictor of prognosis even after adjustment for the invasively determined variables, ejection fraction and number of obstructed coronary arteries.[22]

In conclusion, quantitative measures of the physiologic response to exertion (maximum systolic blood pressure and pressure-rate product) are important prognostic indicators, in addition to both clinical and invasive measures, of cardiac function. However, exertional hypotension, defined as a decrease in exercise systolic blood pressure below resting levels, is too insensitive an indicator of extensive disease or impaired prognosis, or both, to be relied on as a screening test, even though its presence may be ominous.

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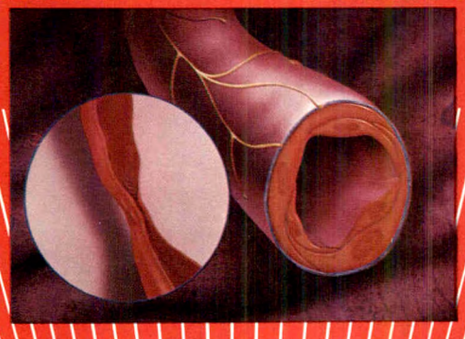

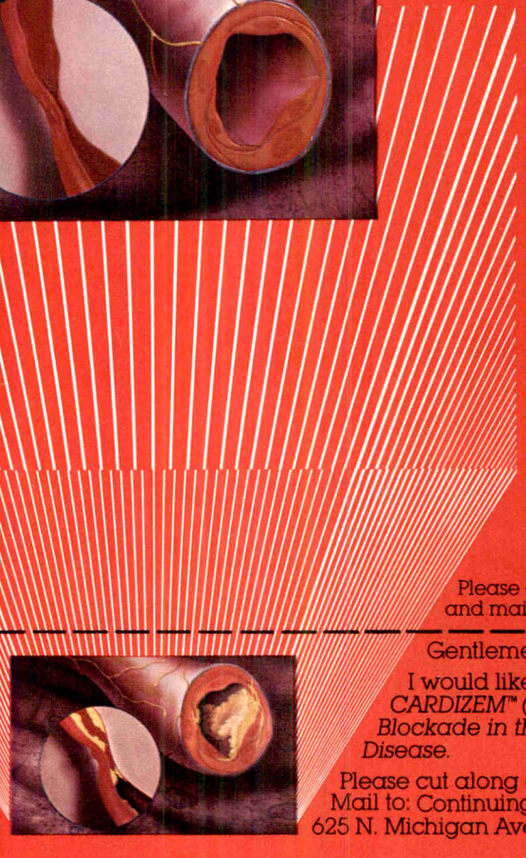

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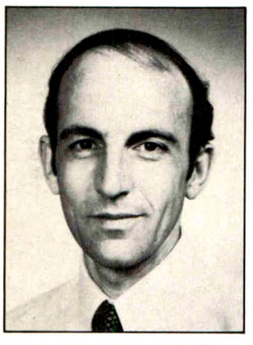

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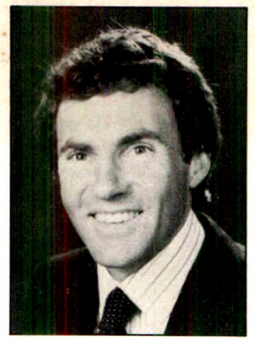

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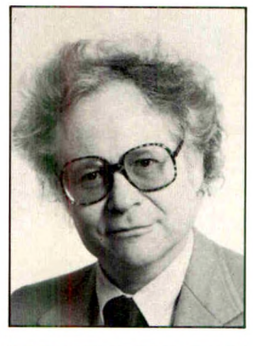

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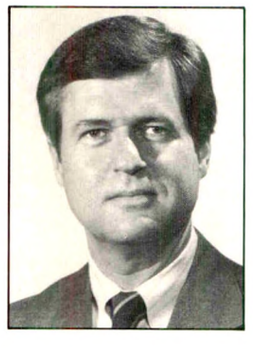

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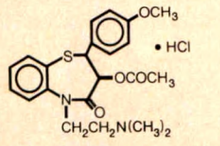
DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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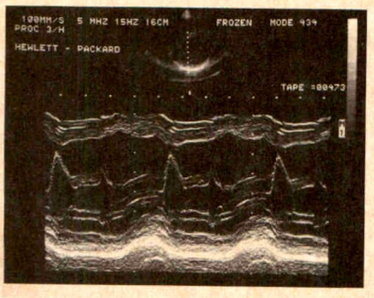

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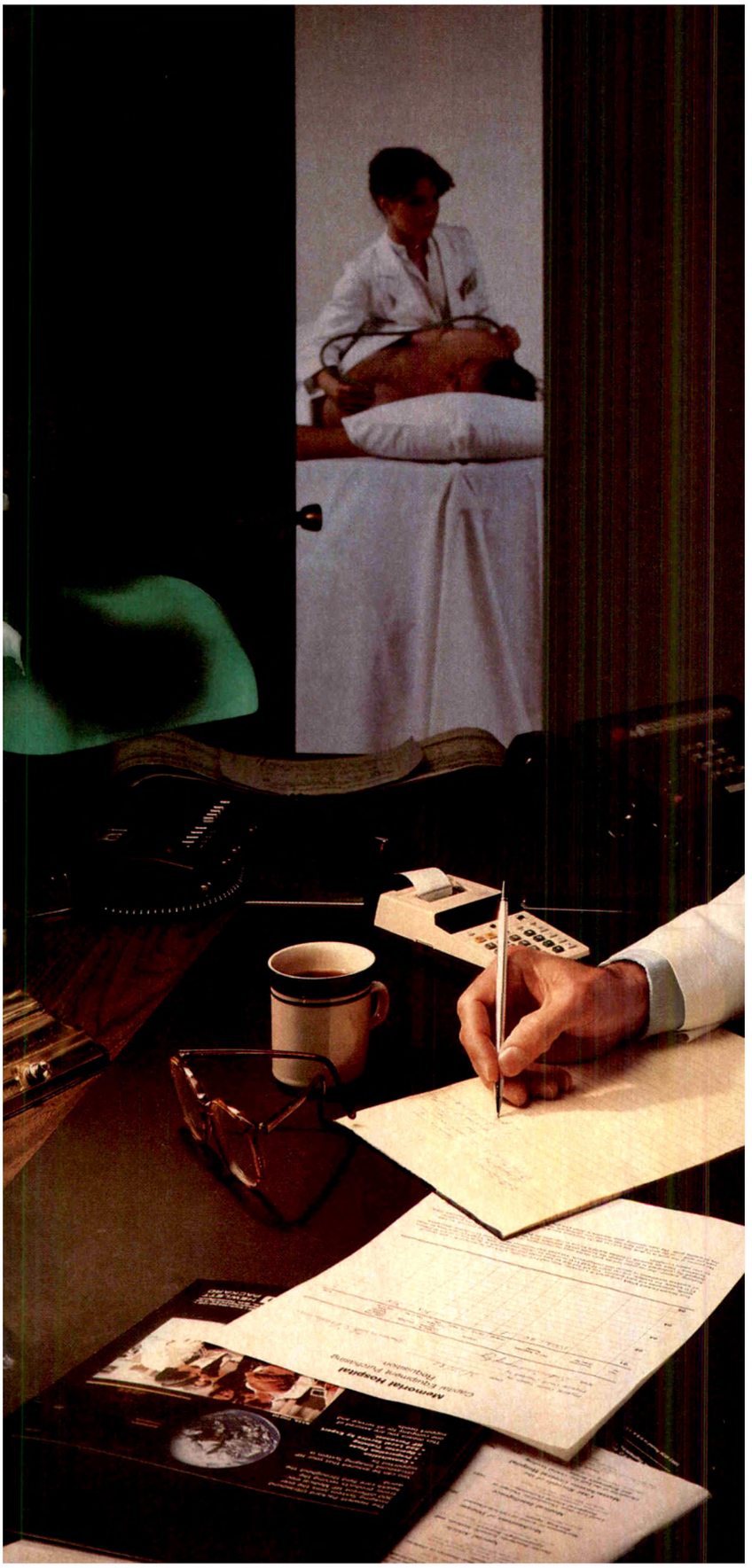
Memorial Hospital
Cancer Equipping Partnership
Registration

Writing with care for CHF:

Avoid any change in the classic digitalis-Lasix® regimen.

BRAND OF (furosemide)

9 out of 10 cardiologists specify LASIX® (furosemide) by brand name.* And 2 out of 3 take the extra step to prevent substitution.*

7 out of 10 cardiologists also specify the leading brand of digoxin.* Both are part of the classic LASIX®-digitalis regimen.

In the same survey,* LASIX® and the leading brand of digoxin were named more often than any other agent, in any therapeutic class, as drugs for which these cardiologists would *never* allow generic substitution. Both were prescribed by brand name more often than any other drug.

LASIX®—specified for good reason.

Especially in CHF, precision is crucial. Any therapeutic variable could easily upset the sensitive digitalis/diuretic/electrolyte balance and precipitate digitalis toxicity.

LASIX®, the most thoroughly documented drug in its class, offers quality so consistent that almost 8 billion tablets have been manufactured without a single product recall. In more dosage strengths and forms than any other diuretic. Good reason for the cardiologists surveyed to say they prescribe LASIX® more frequently than all other diuretic agents they named.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

*National survey of 2960 physicians, including 1502 cardiologists and other physicians subspecializing in cardiology, conducted by Hoechst-Roussel Pharmaceuticals Incorporated, Somerville, New Jersey. August, 1982.

The diuretic of choice in CHF.

LASIX®

20 mg
40 mg
80 mg
Tablets

BRAND OF (FUROSEMIDE)

Rx

Specify LASIX® brand of furosemide. To be sure the patient receives only LASIX®, take the steps necessary on your prescription to prevent substitution, in accordance with the regulations of your state.

Lasix 40mg #60
Sig. 1 b.i.d.
Do Not Substitute

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876

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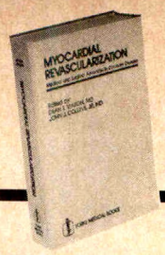
Hoechst



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MYTH: Fluid-filled catheters are an inexpensive and dependable means of measuring patient blood pressure.

FACT: When accurate patient diagnosis is at stake, "inexpensive" can be costly. Catheter-tip pressure transducers give substantially better accuracy and patient information at a *lower cost per use.*

There is a myth in the medical community that fluid-filled catheters are less expensive to use than catheter-tip pressure transducers.

But that myth is deceiving. The purchase price of a fluid-filled, disposable catheter can be one-seventh that of a reusable, catheter-tip pressure transducer.[1] But the catheter-tip pressure transducer can often give you twenty-five or more uses.[2] So, when the cost of use and not just the purchase price alone is examined, the "more expensive" catheter-tip pressure transducer is actually about half the cost per use of the fluid-filled catheter.

[1]Based on a Millar catheter-tip pressure transducer (Model PC-350).

[2]With the Millar MIKRO-TIP® pressure transducer with the new MT-10™ sensor, multiple usage is greatly increased. The new MT-10™ sensor sets the standard for ruggedness and durability in catheter-tip pressure transducers.

Accuracy and dependability bring the true cost of a catheter-tip pressure transducer even lower. With Millar MIKRO-TIP® catheter-tip transducers, you get an accurate reading the first time. Valuable man-hours are saved, and even more savings are available due to the increased number of measurements that can be performed.

With Millar MIKRO-TIP® catheter-tip transducers, you can forget:

- Time-consuming debubbling[3] of the measuring system before catherization can begin
- Contending with a complicated, often messy, and usually inconvenient fluid-filled system
- Damping of the pressure signal due to changes of the fluid in the tubes, or air infiltration of the system
- Disturbance of the signal and, consequently, less accurate blood pressure measurements caused by the position of the transducer or movement of the patient

What you can depend on is easy-to-use, consistent, dependable, accurate readings of blood pressure — at the source — and at a cost per use much lower than you've been led to believe.

[3]i.e. debubbling tubing, stopcock connection, etc.

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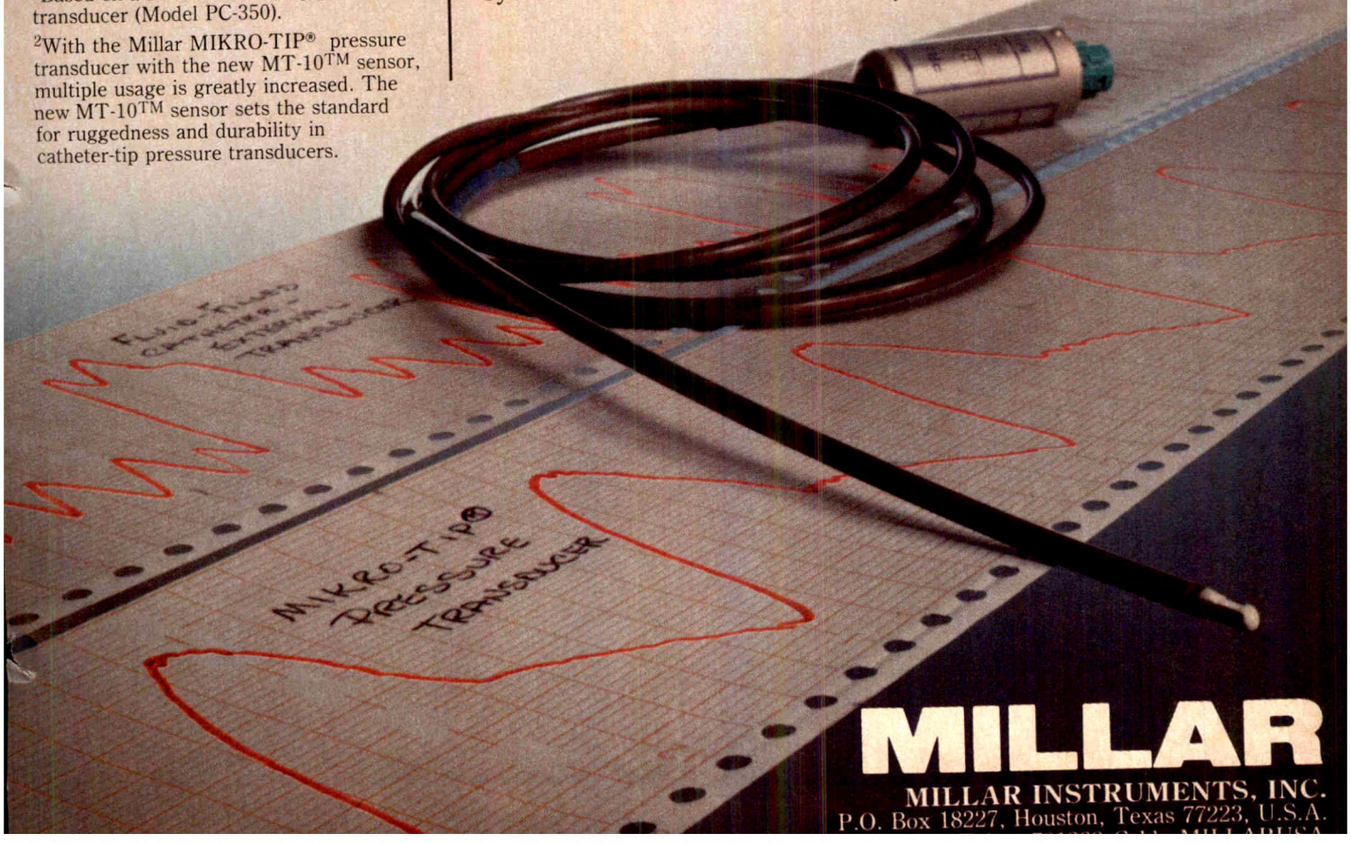

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P.O. Box 18227, Houston, Texas 77223, U.S.A.

65
hours
mean half-life
(N_1-desalkyl
flurazepam)
Some benzodiazepine hypnotics have too long a half-life
Too long a half-life may lead to:
• drug accumulation
• hangover/daytime drowsiness
• interaction with other agents
Some benzodiazepine hypnotics have too short a half-life
Too short a half-life may lead to:
• nocturnal awakenings
• early-morning awakenings
• anterograde amnesia
3
hours
mean half-life

Restful sleep, alert awakening

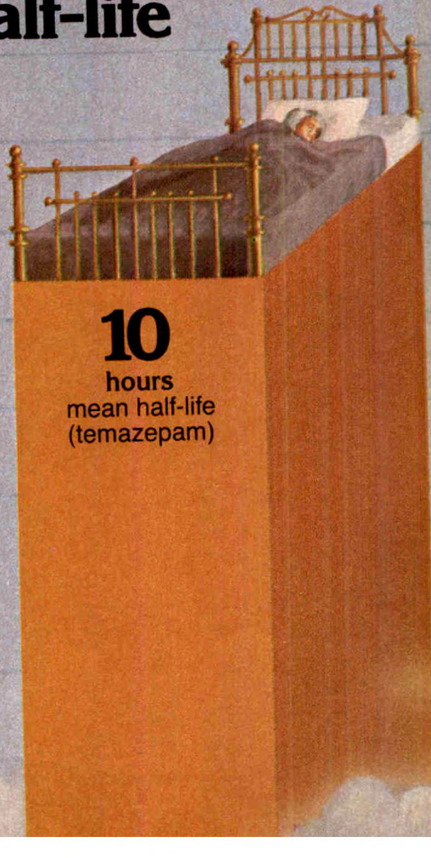
RESTORIL®

(temazepam)

C IV

15 mg
30 mg
capsules

RESTORIL®
(temazepam)
has an appropriate half-life



A half-life (mean of 10 hours) that parallels normal sleep time:

- patient gets 7-8 hours sleep
- most medication gone by morning
- patient awakes alert and refreshed
- minimal side effects
- insignificant accumulation

...prescribing information on next page.

Restful sleep, alert awakening

RESTORIL®

15 mg
30 mg
capsules

(temazepam)

A more appropriate half-life

One 30-mg capsule, h.s.—*usual adult dosage.*
One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

DOSAGE AND ADMINISTRATION: *Adults:* 30 mg usual dosage before retiring; 15 mg may suffice in some. *Elderly and/or debilitated:* 15 mg recommended initially until individual response is determined.

SUPPLIED: Restoril (temazepam) capsules—15 mg maroon and pink, imprinted "RESTORIL 15 mg"; 30 mg, maroon and blue, imprinted "RESTORIL 30 mg". Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous reverse-numbered roll of sealed blisters). (RES-Z2 11/1/81)

Before prescribing, see package insert for full product information.

RES-183-2

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

NITRODISC™

(NITROGLYCERIN)

5 mg/24 hr
10 mg/24 hr discs

DESCRIPTION: Nitrodisc incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths which release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: Nitrodisc should be applied once each day. To use Nitrodisc, follow the instructions on the package. Nitrodisc should be applied to an intact skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new Nitrodisc should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller Nitrodisc, and that the larger Nitrodisc be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

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Searle Pharmaceuticals Inc.
Box 5110, Chicago IL 60680

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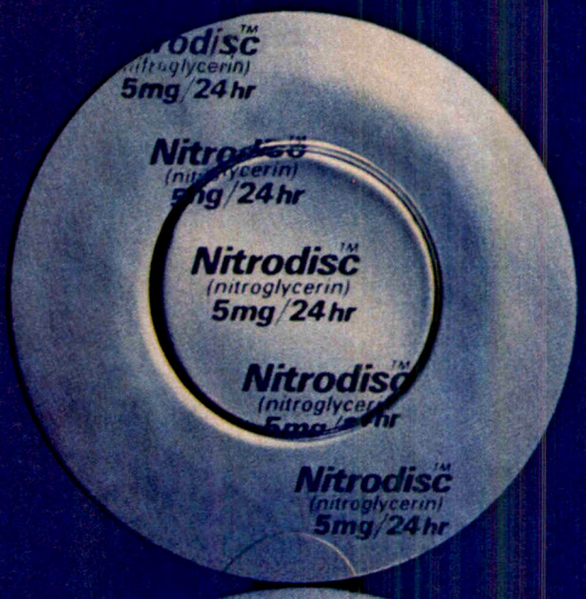

5 mg/24 hr 10 mg/24 hr discs

NITRODISC™

(NITROGLYCERIN)

SEARLE

Contraindications for nitroglycerin include increased intraocular pressure. Side effects include headache, hypotension, flushing, and dizziness. In terminating treatment, both the dosage and frequency of application must be gradually

Please see the preceding page for a brief summary of the complete prescribing

THE NEW QUANTUM™ PACEMAKER

8mm THIN

And in better shape than ever.

MORE PHYSIOLOGICALLY COMPATIBLE SHAPE.
The new thin oval shape of the model 253-19 unipolar Quantum is designed to fit more comfortably into a smaller pocket with less tissue irritation. No upward cut into the fascia is necessary, and the pacemaker stays more securely in place.

LESS HASSLE—A NEW INTER-LOCK™ LEAD CONNECTOR SYSTEM.
The model 253-19 incorporates the innovative Inter-Lock™ lead connector system. This new, easy-to-use system requires no set screw assembly and allows leads to connect quickly and easily into place without the handling of loose screws or caps.

SMALLER SIZE, SAME FULL QUANTUM CAPABILITIES.
The model 253-19 unipolar Quantum 8mm features the same advanced measured telemetry, full multiprogrammability and transtelephonic capabilities as our other Quantum pacemakers.

The new, more convenient unit houses the same proven circuitry that makes Quantum a complete patient management system. Over 10,000 prescription programming combinations plus measured telemetry allow the physician to adjust the pacemaker to the patient's changing needs. Both operating and programmed data are available in digital read-out or hard copy form to help in making better, faster clinical decisions.

The unique new connector system, plus the thinner, lighter, more physiologically compatible shape of the new Quantum pacemaker, is another example of Intermedics' commitment aiding the physician in providing better patient care. As part the complete Quantum Pacing System, the 8mm thin model 253-19 represents continuing progress in technological advancements for better patient management.

QUANTUM INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacing are increasing as pacemakers become more sophisticated and as advance methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include, but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resista sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting st symptoms as intractable, recurrent congestive heart failure; cerebral or renal insufficiency; or recurrent drug- resistant tachyarrhythmias, and who have been shown to benefit from temporary cardiac pacing, are conside candidates for permanent cardiac pacing.

The indications for permanent pacing in cases of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, the mechanism of arrhythmias, and response to therapy. In general, symptomati drug-resistant bradyarrhythmias that impair cardiac output are considered indications for pacing in patients v acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rat

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Toll Free: 800/231-2330 Texas: 800/392-3726

Effects of a Cardioselective Beta$_1$ Partial Agonist (Corwin) On Left Ventricular Function and Myocardial Metabolism in Patients With Previous Myocardial Infarction

MICHEL F. ROUSSEAU, MD, HUBERT POULEUR, MD,
and MARIE-FRANÇOISE VINCENT, MD

Corwin is a new selective beta$_1$ partial agonist, able to stabilize the beta$_1$ adrenoceptors at approximately 43% of their maximal activity. The aim of the study was to determine the effects of this agent in patients with coronary artery disease (CAD) and previous myocardial infarction (MI). In a first group of 14 patients, corwin increased significantly the peak (+)dP/dt (+35%; $p < 0.005$), the global ejection fraction, and the ejection fraction of abnormally contracting segments (from 20 ± 18 to 26 ± 19%; $p < 0.02$). Corwin also induced significant decreases in mean systolic (−8%; $p < 0.05$) and mean diastolic (−38%; $p < 0.001$) wall stress and accelerated the relaxation rate. In a second group of 11 patients, a metabolic study indicated that neither myocardial oxygen consumption (15 ± 7 versus 15 ± 7 ml/min; difference not significant) nor lactate extraction was modified by the drug. In this group, increases in peak (+)dP/dt, acceleration in ventricular relaxation (−8 ms in time constant of isovolumic pressure decrease; $p < 0.01$), and decreases in left ventricular end-diastolic pressure also were noted after administration of corwin, both under basal conditions and during a cold pressor test. In conclusion, corwin is a positive inotrope which, in patients with CAD and left ventricular dysfunction, improves left ventricular systolic and diastolic function without inducing myocardial ischemia.

Impairment in left ventricular (LV) systolic and diastolic performance is common in patients with coronary artery disease (CAD),[1] but the optimal medical management of such abnormalities still remains to be defined. Indeed, inotropic agents such as catecholamines are frequently deleterious when oxygen supply is limited,[2–4] and potentially harmful side effects have also been reported with digitalis[5] and vasodilators[6] in this setting.

Recently, as a possible safe alternative to cardiac glycosides and catecholamines, an orally active beta$_1$ adrenoceptor agonist (ICI 118,587,* corwin) has been developed.[7–10] When compared with epinephrine, this compound has 2 major differences. First, it is devoid of beta$_2$ vasodilator effects and of metabolic effects such as effects on glucose metabolism.[7,8] Second, corwin is only a partial beta$_1$ agonist. A partial agonist is a compound that possesses both agonist and antagonist properties.[11] In terms of its intrinsic sympathomimetic activity, a partial agonist is only able to produce a fraction (approximately 43% in the case of corwin) of the maximal response of a full agonist such as isoprenaline. Conversely, in the presence of a sufficient concentration of a partial agonist, the effects of a full agonist will be antagonized. Therefore, because of these characteristics it appeared that corwin might improve the function of the chronically ischemic myocardium, which is likely to be depleted in catecholamines,[12] while minimally affecting the normal myocardium.

Furthermore, because corwin narrows the range over which the sympathetic nerves may modulate cardiac

From the Departments of Cardiology and Physiology and the International Institute of Cellular and Molecular Pathology, University of Louvain, School of Medicine, Brussels, Belgium. This study was supported in part by Grant 3.454082 from Fonds de la Recherche Scientifique Médicale, Brussels, Belgium. Dr. Vincente is an aspirant du Fonds National de la Recherche Scientifique Belge. Manuscript received September 14, 1982; revised manuscript received January 11, 1983, accepted January 20, 1983.

Address for reprints: Michel F. Rousseau, MD, Division of Cardiology, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 55/5550, B-1200, Brussels, Belgium.

* (±)-1-(4-hydroxyphenoxy)-3-[2-(4-morpholinecarboxamido)ethylamino]-propan-2-ol, hemifumarate.

function,[7,9] it could also be useful each time sympathetic drive is inadequate. This situation may occur not only during sleep, when a low sympathetic stimulation frequently exacerbates heart failure, but also during exercise or emotion; indeed, in some patients an excessive sympathetic tone during exercise may be responsible for inappropriate tachycardia and myocardial ischemia. Therefore, the aim of the present study was to determine first whether corwin could significantly improve LV systolic and diastolic function in patients with a previous myocardial infarction (MI). In addition, considering the importance of the balance between oxygen supply and demand in this setting, the metabolic effects of corwin were also analyzed both under basal conditions and when the heart was stressed by a cold pressor test. The results suggest that this compound can improve cardiac function without inducing myocardial ischemia.

Methods

Twenty-five patients with significant CAD and a previous MI were included in this study. All were in sinus rhythm and underwent diagnostic cardiac catheterization; none had valvular disease. Clinical data, MI location on electrocardiography, and angiographic data are listed in Table I. All cardioactive drugs, listed in Table I, were discontinued at least 72 hours before the procedure. Each patient gave informed consent, and no complication resulted from this study.

Two experimental protocols were used. In protocol I, the effects of corwin on LV systolic and diastolic function were assessed in 14 consecutive patients (patients 1 to 14 in Table I) using LV angiography. In protocol II, performed in 11 consecutive patients with anterior MI (patients 15 to 25 in Table I), the changes in coronary blood flow, myocardial oxygen consumption, and lactate and hypoxanthine extraction together with the changes in plasma epinephrine and norepinephrine were determined before and after administration of corwin, both under basal conditions and during a cold pressor test. Patients with anterior MI were selected for this protocol to ensure that the blood samplings and flow measurements made in the coronary sinus were representative of myocardial areas with perfusion defects.

Experimental protocol I: Left heart catheterization was performed using the femoral approach with the patient in the fasting state and without premedication. High fidelity LV pressures were recorded with a 5Fr micromanometer-tipped catheter (Millar Instruments). Aortic pressure was measured through an 8Fr pigtail catheter connected to a Statham P23ID strain gauge. Hemodynamic data were first measured under basal conditions. Then, control left ventriculography was performed using single plane 35 mm cineangiography at 50 frames/s in the right anterior oblique projection (Philips Poly-Diagnost C). The hemodynamic variables and a cineangiographic frame marker were recorded on magnetic tape (Honeywell 101) and on paper (Honeywell 1858).

Five minutes after control ventriculography, 0.1 mg/kg of corwin was injected intravenously over a 5-minute period. Hemodynamic variables were recorded 15 minutes after the end of corwin administration. Studies in healthy volunteers have indeed shown that peak inotropic effects were already reached at this time and were thereafter maintained for 4 to 6 hours.[10] A second ventriculographic procedure was performed 25 minutes after the first, when the depressant effect of contrast material should have disappeared. After this procedure, coronary arteriography was performed using the Judkins technique.

Measurements and computations of protocol I: Analog data filtered at 100 Hz were digitized every 2 ms and processed off-line by means of a Hewlett-Packard 2113E computer. The first derivative of the LV pressure was computed after digital filtering with a recursive method implementing a sixth order Butterworth type low-pass filter with a band width of 50 Hz (−3 db). Specific points on the signals (such as the peak of the R wave) were automatically detected during at least 3 respiratory cycles, and to minimize respiratory effects, hemodynamic measurements were made at end-expiration. The time constant T_1 of the exponential LV pressure decrease during the first 40 ms after peak (−)dP/dt was used as an index of isovolumic LV relaxation.[13]

The technique used to analyze LV angiograms was previously reported in detail.[14,15] Midwall circumferential stress was calculated by the formula of Sandler and Dodge[15]: Stress = $[Pb/H]\ [1 - b^3/a^2\ (2b + H)]$, where P = LV pressure, H = wall thickness, a mid-wall semimajor axis, and b = mid-wall semiminor axis. Ejection fraction and mean velocity of fiber shortening were calculated according to the standard formula. Volume data were corrected for body surface area, and end-systolic or end-diastolic volumes were defined, respectively, as the smallest and largest LV volumes obtained. Mean systolic wall stress was determined by averaging the data from the start to the end of the ejection, and mean diastolic wall stress was obtained by averaging the data from the start of ventricular filling to the peak of the R wave.

To assess the LV properties during early diastolic filling, angiographic and hemodynamic data were also analyzed during the period of decreasing ventricular elastance, that is, when the LV pressure is decreasing or remaining constant despite an increase in ventricular volume. To evaluate the ventricular elastance during this phase and to allow comparisons before and after corwin administration, a standardized incremental LV elastance ($\Delta P/\Delta V$, units: mm Hg/ml/m^2) was computed as described previously.[14]

To evaluate regional systolic function, the end-diastolic and end-systolic silhouettes were superimposed by aligning the long axis (mid-aortic valve to apex) and fixing the center of gravity. Five angular segments were defined from this midpoint, beginning at the left aortic valve margin. The change of area of each segment, corresponding to a segmental ejection fraction, was determined as follows: (end-diastolic area − end-systolic area)/(end-diastolic area) × 100. The normal range of segmental ejection fraction for each segment was determined in a group of 15 normal subjects. This normal group was previously reported,[15] and these normal values were used to classify the segmental ejection fraction of the present patients as normal (included within the normal range) or abnormal (below the lowest normal limit).

Experimental protocol II: Left heart catheterization and hemodynamic data analysis were performed as in protocol I. In addition, a 7Fr Swan-Ganz thermodilution catheter (Webster Laboratories) was placed in the mid-coronary sinus through an antecubital vein. The position of this catheter was confirmed angiographically and by oxygen saturation (average 4.7 ml/100 ml, range 2.8 to 7.1) and checked regularly with fluoroscopy. Coronary sinus flow was measured by the continuous thermodilution method of Ganz et al.[16] Heart rate, LV and aortic pressure, and coronary sinus blood flow were continuously recorded first under control conditions and during a cold pressor test (patient's hand immersed in ice water for 3 minutes). When hemodynamic data had returned to basal values, corwin (0.1 mg/kg) was given as described. Fifteen minutes after the end of corwin injection, data were again recorded under basal conditions and a similar cold pressor test was performed (Fig. 1). Arterial and coronary venous blood were drawn during each step. During both cold

TABLE I Clinical and Angiographic Data

Patient	Age (yr) & Sex	MI Location	LVEDP (mm Hg)	EF (%)	First-Third EF (%)	Mean VCF (circ/s)	Coronary Arteriography 1VD	2VD	3VD	Left Ventriculography	Therapy Before Study
1	54M	Anterior	3	66	18	1.39	−	−	+	Ant apic hyp	ISD, NIF, PRO
2	51M	Inferior	5	42	16	0.65	+	−	−	Inf akin	. . .
3	41M	Anterior	8	52	25	0.69	+	−	−	Ant apic akin	DIP
4	54M	Anterior	18	42	16	0.74	−	−	+	Ant apic dysk	ISD, PRO
5	39M	Anterior	17	48	18	1.03	+	−	−	Ant apic akin	. . .
6	61M	Inferior	12	47	19	0.42	−	−	+	Inf akin	ISD, NTG
7	53M	Anterior	6	61	26	1.04	−	+	−	Ant apic akin	NTG, PRO
8	42M	Inferior	3	59	19	1.09	−	−	+	Inf akin	ISD, PRO
9	37M	Inferior	23	69	29	0.99	−	−	+	Inf akin	ISD, PRO
10	48F	Anterior	5	66	21	1.69	+	−	−	Apic akin	ISD, PRO
11	47M	Inferior	15	67	26	1.24	+	−	−	Inf akin	. . .
12	42M	Anterior	28	54	19	1.51	+	−	−	Ant apic dysk	ISD
13	56M	Inferior	20	54	17	1.15	−	−	+	Inf apic akin	ISD, NIF, PRO
14	57M	Inferior	11	65	13	1.28	−	+	−	Inf akin	ISD
15	37M	Anterior	22	51	. . .	1.01	−	+	−	Ant apic akin	ISD
16	55M	Anterior + Inferior	16	55	. . .	1.08	−	−	+	Inf apic akin Ant hyp	ISD, PRO
17	47M	Anterior + Inferior	48	26	. . .	0.18	−	−	+	Ant akin Dysk apic Inf akin	NIF, DIU
18	46M	Anterior	24	33	. . .	0.36	−	−	+	Ant aneur	ISD, PRO
19	57M	Anterior	15	60	. . .	0.93	−	+	−	Ant hyp	ISD
20	42M	Anterior	9	40	. . .	0.80	+	−	−	Ant apic akin	ISD, DIP
21	48M	Anterior	18	62	. . .	1.27	+	−	−	Ant apic hyp	ISD
22	59M	Anterior + Inferior	42	30	. . .	0.64	−	+	−	Ant akin Inf akin	ISD, NIF, PRO
23	40M	Anterior	22	53	. . .	0.92	−	+	−	Ant apic aneur	. . .
24	59M	Anterior	40	42	. . .	0.48	+	−	−	Ant apic aneur	ISD
25	48F	Anterior	19	44	. . .	0.73	+	−	−	Ant akin	ISD, NIF, PRO

Aneur = aneurysm; Ant apic akin = anteroapical akinesia; Ant apic dysk = anteroapical dyskinesia; Ant apic hyp = anteroapical hypokinesia; DIP = dipyridamole; DIU = diuretic; EF = ejection fraction; First-third EF = ejection fraction during the first third of ejection; Inf akin = inferior akinesia; Inf apic akin = inferoapical akinesia; ISD = isosorbide dinitrate; LVEDP = left ventricular end-diastolic pressure (peak R wave, end-expiration); Mean VCF = mean velocity of fiber shortening; MI = myocardial infarction; NIF = nifedipine; NTG = nitroglycerin; PRO = propranolol; 1VD = 1-vessel disease; 2VD = 2-vessel disease; 3VD = 3-vessel disease.

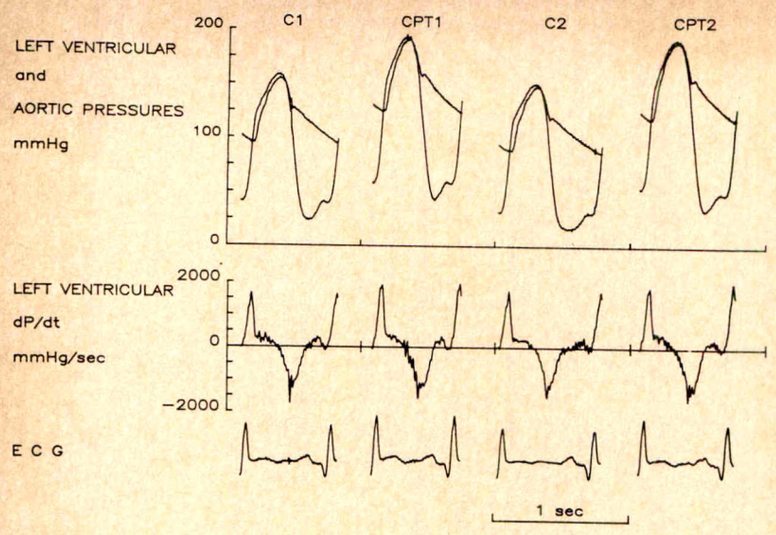


FIGURE 1. Effects of corwin in a patient with anterio infarction and poor left ventricular function (patient 17 i Table I). C_1 and CPT_1 = control and control cold presso test; C_2 and CPT_2 = control and cold pressor test afte treatment with corwin. The treatment with corwin clearl decreased left ventricular pressure during diastole. Val ues of peak (+)dP/dt were, respectively: 1,657, 1,923 1,737, and 1,843 mm Hg/s. All beats were selected a end-expiration. ECG = electrocardiogram.

pressor tests, the presented hemodynamic data were obtained at the end of the first minute, just before blood sampling.

Biochemical measurements: For lactate and hypoxanthine measurements, 3 ml of whole blood was deproteinized immediately with an equal volume of ice-cold 10% (weight/volume) $HClO_4$ containing 0.6 nmol of (8-^{14}C) hypoxanthine. Lactate was determined according to Hohorst.[17] Hypoxanthine measurements were performed by high-performance liquid chromatography.[18] Plasma for catecholamine assay was immediately frozen and catecholamines were measured as described by Mefford et al.[19]

Statistical analysis: Comparison of the data of protocol I before and after corwin was performed using a paired *t* test. Comparison of the serial data of protocol II was performed using repeated-measure analysis of variance.[20]

Results

Protocol I: LV function: Table II summarizes the effects of corwin on LV systolic function. After corwin, the heart rate increased slightly in 9 patients (+6 beats/min for the whole group; $p < 0.05$) and peak (+)dP/dt increased in all patients from 1,732 to 2,334 mm Hg/s ($p < 0.005$). LV end-diastolic pressure declined in 8 patients, whereas end-diastolic volume decreased in 9; at the group level, these changes were insignificant. End-systolic volume index decreased from 58 to 53 ml/m^2 ($p < 0.05$) and the global ejection fraction was moderately improved. A small decrease in mean systolic wall stress (−8%; $p < 0.05$) was also noted despite a trend toward increasing LV systolic pressure.

Figure 2 illustrates 2 typical examples of the changes in wall motion after corwin administration. The changes in global ejection fraction generally were attended by an increase in segmental ejection fraction in the abnormal segments, but a decrease in the percentage of shortening of normal areas was sometimes observed. Therefore, in individual patients, it was very difficult to determine which changes corresponded to a real deterioration or improvement and which were artifacts (such as noise on LV silhouette or displacement of the reference point). To minimize the artifacts, therefore, the segments were pooled according to their classification as normal or abnormal. When all normal segments were pooled, no change in segmental ejection fraction was evident: 55 ± 14% during control versus 56 ± 17% after corwin administration (n = 43 normal segments; difference not significant [NS]). In contrast, the segmental ejection fraction of the pooled abnormal segments was significantly increased from 20 ± 18% to 26 ± 19% (n = 27 abnormal segments; $p < 0.02$).

Corwin also ameliorated LV relaxation as indicated by a faster rate of isovolumic pressure decrease (peak [−]dP/dt and T_1: Table III) and by a 38% decrease in mean diastolic wall stress ($p < 0.001$). Incremental LV elastance during early filling was impaired under basal conditions (−0.48 mm Hg/ml/m^2 versus −0.95 in normal subjects; $p < 0.01$)[14] but returned to normal values after corwin administration (Table III).

After corwin administration, the cardiac output values derived from angiographic data increased in the whole group by 9% ($p < 0.05$); patients with an ejection

TABLE II Systolic Left Ventricular Function Before and After Administration of Corwin (ICI 118,587)

	HR (beats/min)	LVEDP (mm Hg)	LVSP (mm Hg)	Peak (+)dP/dt (mm Hg/s)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	Mean VCF (circ/s)	Mean Systolic Wall Stress (kdyne/cm^2)
Control (n = 14)	78 ± 14	12.4 ± 7.9	137 ± 18	1,732 ± 383	127 ± 43	58 ± 32	56.6 ± 9.5	1.07 ± 0.35	364 ± 95
Corwin (n = 14)	84 ± 14	12.3 ± 9.0	143 ± 17	2,334 ± 472	123 ± 44	53 ± 32	59.4 ± 11.3	1.21 ± 0.51	337 ± 81
p value	0.05	NS	0.1	0.005	0.1	0.05	0.05	0.1	0.05

Values are mean ± standard deviation.
EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; mean VCF = mean velocity of fiber shortening.

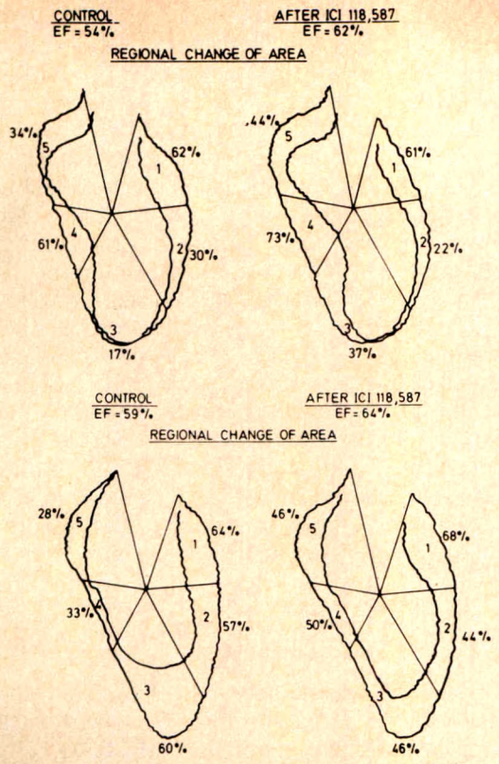


FIGURE 2. Typical changes in wall motion induced by corwin (ICI) in a patient with anterior myocardial infarction (**upper panel**) and in another patient with inferior myocardial infarction (**lower panel**). EF = ejection fraction.

fraction <55% tended to have a greater increase in output (+23%) than did those with a normal ejection fraction. The increase in cardiac output was confirmed by direct measurement (Fick principle) in 4 patients with depressed ejection fraction; cardiac index increased in all from 2.9 ± 0.8 to 3.9 ± 0.9 liters/min/m^2. No significant changes in mean aortic pressure (96 ± 9 versus 104 ± 13 mm Hg; NS) or diastolic aortic pressure (68 ± 12 versus 74 ± 8 mm Hg; NS) were noted. Calculated systemic vascular resistance decreased from 1,467 ± 459 to 1,160 ± 200 dynes·s/cm^5 ($p < 0.05$).

Protocol II: myocardial metabolism: An example of the hemodynamic changes observed in this protocol is given in Figure 1, and Table IV summarizes hemodynamic and metabolic changes both under basal conditions and during the cold pressor tests.

As in the first protocol, corwin significantly increased peak (+)dP/dt and accelerated LV relaxation under control conditions. In this group, heart rate increased in only 5 patients and decreased in 6. Interestingly, the patients who had an increase in heart rate had the lowest resting rates: 71 ± 14 versus 80 ± 14 beats/min ($p < 0.05$). LV end-diastolic pressure decreased in all patients an average of 6.3 mm Hg ($p < 0.01$). Beneficial effects on LV performance were also present during the cold pressor test. Indeed, corwin allowed the left ventricle to meet the same pressure load at a markedly lower end-diastolic pressure (22.9 versus 31.4 mm Hg; $p < 0.05$) than during the control cold pressor test. Peak (+)dP/dt and relaxation were also significantly im-

TABLE III Diastolic Left Ventricular Function Before and After Administration of Corwin (ICI 118,587)

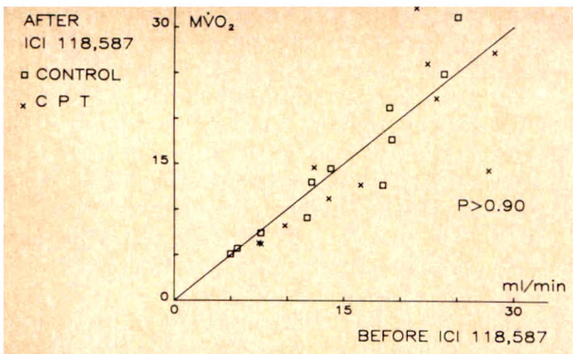
	Peak (−)dP/dt (mm Hg/s)	T_1 (ms)	Mean Diastolic Wall Stress (kdyne/cm^2)	Incremental LV Elastance (mm Hg/ml/m^2)
Control (n = 14)	1,990 ± 418	47 ± 11	37 ± 21	−0.48 ± 0.41
Corwin (n = 14)	2,270 ± 423	39 ± 10	23 ± 13	−0.76 ± 0.50
p value	0.05	0.01	0.001	0.005

Values are mean ± standard deviation.
LV = left ventricular; T_1 = time constant of isovolumic pressure decrease (see Methods section for definition).

TABLE IV Changes in Myocardial Metabolism After Administration of Corwin (ICI 118,587)

	Control	CPT Control	Control Corwin	CPT Corwin
Heart rate (beats/min)	80 ± 13	83 ± 15	80 ± 13	78 ± 11
LVEDP (mm Hg)	25.7 ± 12.8	31.4 ± 18.2*	19.4 ± 11.0†	22.9 ± 15.3‡
LVSP (mm Hg)	138 ± 28	155 ± 30†	141 ± 28	154 ± 28*
Peak (+)dP/dt (mm Hg/s)	1,605 ± 296	1,639 ± 253	1,872 ± 394*	1,964 ± 400†,§
T_1 (ms)	62 ± 18	67 ± 20	54 ± 16†	56 ± 19*,§
Mean AoP (mm Hg)	103 ± 16	117 ± 19*	104 ± 16	115 ± 20*
CBF (ml/min)	110 ± 51	129 ± 53	113 ± 61	129 ± 70
CVR (mm Hg·ml^{-1}·min)	1.03 ± 0.39	0.97 ± 0.32	1.04 ± 0.38	1.04 ± 0.44
MVO_2 (ml/min)	14.6 ± 7.0	17.3 ± 7.7	14.6 ± 7.0	16.5 ± 9.0
Lactate E (%)	23 ± 21	30 ± 19	17 ± 22	24 ± 16
CS hypoxanthine (nmol/ml)	1.16 ± 0.83	0.99 ± 0.76	0.75 ± 0.41	0.98 ± 0.98

Values are mean ± standard deviation; n = 11.
* $p < 0.05$ versus control.
† $p < 0.01$ versus control.
‡ $p < 0.01$ CPT control versus CPT corwin.
§ $p < 0.05$ CPT control versus CPT corwin.
AoP = aortic pressure; CBF = coronary blood flow; CPT = cold pressor test; CS hypoxanthine = coronary sinus hypoxanthine; CVR = coronary vascular resistance; Lactate E = lactate extraction; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MVO_2 = myocardial oxygen consumption; T_1 = time constant of isovolumic pressure decrease.



IGURE 3. Individual values of myocardial oxygen consumption ($M\dot{V}O_2$) efore and after administration of corwin (ICI). CPT = cold pressor ıst.

roved when this maneuver was performed after corwin dministration (Table IV).

No significant change in coronary blood flow or resistance was observed after corwin administration. As own in Figure 3, myocardial oxygen consumption was mparable before and after the drug. The severity of ıe coronary lesions did not seem to influence the results. After corwin administration, arterial lactate decined in 9 patients, remained constant in 1, and increased from 403 to 577 nmol/ml in the last patient. Thus, there was a tendency for arterial lactate to decrease after the drug (from 582 ± 129 to 526 ± 108 mol/ml; $p < 0.08$). Despite this reduction in lactate vailability, no significant change in myocardial lactate xtraction or consumption was observed (Table IV). It ıould be emphasized that lactate production was not bserved after corwin administration in any patient. inally, no change in hypoxanthine levels was noted in ıe coronary sinus after the drug (Table IV), and the rteriovenous difference in hypoxanthine also remained :able (average 0.018 ± 0.48 nmol/ml before and 0.052 0.50 after the drug; NS).

Arterial plasma levels of norepinephrine obtained in) patients averaged 1.45 ± 0.71 pmol/ml under basal nditions and were not modified after corwin administration (1.52 ± 0.95 pmol/ml; NS). Arterial norepiephrine levels increased in 9 of 10 patients during the ntrol cold pressor test to 2.16 ± 1.44 pmol/ml ($p < 0.1$ ersus control) and to 2.19 ± 1.44 pmol/ml ($p < 0.1$ ersus control) during the corwin cold pressor test. The ntrol myocardial arteriovenous difference in norepiephrine averaged −0.43 ± 0.92 pmol/ml, with 6 paents showing myocardial release of norepinephrine. fter corwin administration, this arteriovenous difrence increased in all patients up to 0.31 ± 0.84 mol/ml. Arterial plasma epinephrine was stable during ıe 4 successive steps of the protocol (0.78 ± 0.39; 0.83 0.41; 0.83 ± 0.41, and 0.91 ± 0.49 pmol/ml; NS) and change in myocardial arteriovenous difference was bserved.

Comparison of the response to corwin in protools I and II: Despite the fact that consecutive patients ere studied, global LV function appeared more dressed in the patients in protocol II. Indeed, patients in protocol II had generally higher end-diastolic pressure and lower ejection fraction than did patients in protocol I. To ensure that corwin had produced comparable effects in both situations, a separate analysis was performed, considering only the response of patients with an ejection fraction of 40 to 55%. Seven patients in protocol I (mean control ejection fraction 48 ± 6%, increasing significantly to 53 ± 7% after corwin) were thus compared with 6 patients in protocol II (mean control ejection fraction (48 ± 6%). When the data of such patients with similar LV dysfunction were considered, corwin evidently had produced similar increases in peak (+)dP/dt (+477 ± 358 versus +440 ± 250 mm Hg/s; group I versus group II: NS) and an identical acceleration in relaxation rate (T_1 −9 ms in both groups) in the 2 experimental protocols. Furthermore, LV end-diastolic pressure declined in all 6 patients in group II and in 5 of the 7 patients in group I, and the absolute changes in end-diastolic pressure were not significantly different (−6 ± 5 versus −2 ± 4 mm Hg; NS).

Discussion

Our data indicate that corwin is a positive inotrope that improves LV function in patients with ischemic heart disease without significant effects on coronary blood flow or myocardial metabolism.

Effects of corwin on LV inotropic state: The changes in peak (+)dP/dt were used to assess the variations in inotropic state. This index is indeed very sensitive to acute changes in myocardial contractility and is little affected by preload changes.[21] Furthermore, because LV preload never increased after corwin and because peak (+)dP/dt increased even in patients with an unchanged heart rate, the increases in peak (+)dP/dt evidenced after corwin undoubtedly reflect a true positive inotropic effect.[21] Small quantitative variations were observed in the response to corwin: peak (+)dP/dt tended to increase more in protocol I and LV end-diastolic pressure declined more sharply in protocol II. However, such differences disappeared when patients with similar impairment in LV function were compared. Therefore, it is likely that these small variations were caused by the fortuitous discrepancy in ventricular function rather than by a different response to corwin. In addition, the artifactual increase in circulating blood volume caused by the contrast material may also have blunted the filling pressure decrease in protocol I.

In the presence of myocardial infarction and LV dyssynergy, however, peak (+)dP/dt and ejection phase indexes only represent global parameters. Accordingly, such indexes might simply reflect a positive inotropic stimulation of normal areas whereas hypokinetic zones could remain unchanged or even be adversely affected. To evaluate the effects of corwin on chronically ischemic zones, changes in segmental ejection fraction were analyzed. Our results indicate that abnormal sectors were generally improved and that enhanced shortening of the abnormal zones was an important determinant of the improvement in global ejection fraction. Animal experiments have established that excessive inotropic

stimulation frequently results in a functional deterioration of the hypoperfused areas.[2] Although perfect wall motion analyses are difficult in individual subjects, the foregoing results nevertheless suggest that the inotropic stimulation of corwin was sufficiently moderate to avoid such side effects. Finally, this increased inotropic state favorably influenced ventricular geometry during ejection, thereby reducing mean systolic wall stress. Here also we recognize that stress computation is subject to errors in the presence of MI. Accordingly, the stress figures must only be considered as indicative of directional changes.

In our small group of patients, an increase in cardiac output attended by a moderate decrease in systemic vascular resistance was present after corwin administration, and this increase was more evident in patients with abnormal ejection fraction. Similar changes have been reported by Simonsen[22] in patients with moderate heart failure. Nevertheless, others have observed insignificant changes in cardiac output and vascular resistance after administration of this drug to patients with a previous infarct but with normal ventricular function.[23] This last result suggests that the decrease in vascular resistance passively follows the increased flow. Further studies are needed to determine to what extent the cardiac output response is dependent on the degree of impairment in ventricular function.

Effects of corwin on LV relaxation and diastolic filling: Abnormalities in LV relaxation and diastolic filling are common in patients with CAD.[1,13,24] Recent studies have correlated these relaxation abnormalities with the presence of viable but chronically ischemic myocardium.[1,13] Some investigators suggest that these impairments in relaxation not only may decrease coronary perfusion but also may produce clinical manifestations of heart failure by altering ventricular compliance and filling pressures.[25] In this perspective, the effects of corwin on this phase of the cardiac cycle, which are different from those of cardiac glycosides, may be clinically important. First, by facilitating early diastolic filling and by decreasing LV end-diastolic pressure, corwin may reduce signs of pulmonary congestion during stress (Fig. 1) and improve the functional status of the patient. Secondly, by increasing the rate of isovolumic relaxation and by decreasing mean diastolic wall stress, corwin is likely to improve coronary perfusion particularly in the subendocardial layers. This in turn might relieve some myocardial ischemia responsible for impairment in systolic and diastolic function. Therefore, part of the enhanced shortening of hypokinetic areas might be related to this second mechanism rather than to direct inotropic stimulation.

Effects of corwin on myocardial metabolism: An important observation is that corwin neither significantly increased myocardial oxygen consumption nor significantly modified lactate or hypoxanthine metabolism. Several factors may explain the lack of change in oxygen consumption and the absence of ischemia. First, the decrease in mean systolic wall stress contributed to the reduced myocardial oxygen demand and could have compensated for the increase in oxygen demand associated with $beta_1$ stimulation. Second, as discussed herein, coronary perfusion of ischemic areas may have been preserved or even enhanced by the improvement in relaxation and by the decrease in mean diastolic wall stress.[25] This increased coronary perfusion could prevent the development of ischemia and lactate or hypoxanthine production in the abnormal zones. Finally, an important point could be the magnitude of the agonist activity of corwin. Although the dose used was at the top of the dose-response curve in human subjects,[9,10] the increases in peak (+)dP/dt were smaller than those observed with dobutamine[3,4] or prenalterol.[26] Both dobutamine and prenalterol possess greater beta agonist activity but have been shown to increase myocardial oxygen consumption,[3,4,26] which in the case of dobutamine may have been responsible for myocardial ischemia.[3,4] Therefore, the limited inotropic effect of corwin is an important safety factor for future clinical application.

Another property of corwin is its tendency to decrease arterial lactate. This contrasts with the increase in arterial lactate observed during catecholamine administration.[4] This particular property probably resides in its lack of $beta_2$ metabolic effects. One consequence is that the lactate availability as substrate to the heart is reduced, which can explain the discrete, insignificant reduction in lactate extraction.[27] To ensure that such a small reduction in lactate extraction was not related to a limited myocardial ischemia, the hypoxanthine production was also checked. Indeed, previous studies have suggested that hypoxanthine release was sometimes more pronounced than lactate release during ischemia.[28] The absence of any change in hypoxanthine handling further suggests that any significant ischemia can be excluded.

Clinical implications of a selective $beta_1$ partial agonist: Corwin has a dual pharmacologic action, namely, it acts as a $beta_1$ agonist when the sympathetic tone is low and as a $beta_1$ antagonist when the sympathetic tone exceeds its partial agonist activity. In other words, corwin stabilizes the sympathetic stimulation of the heart at a level equal to its partial agonist activity, that is, approximately 43% of the activity of the full agonist isoprenaline.

In severe heart failure refractory to classic therapy, the acute administration of a partial agonist may not bring major advantages over a carefully titrated infusion of a full agonist such as dopamine. The pharmacology of these compounds suggests that they may produce deleterious hemodynamic effects when administered in patients with high plasma levels of catecholamines. Consequently, it is more likely that corwin will be clinically useful primarily in patients with moderate heart failure (class II to III, New York Heart Association), who still have normal plasma concentrations of catecholamines at rest. In this clinical setting, they offer a novel opportunity to stabilize the function of the heart at a level of inotropic stimulation sufficient to keep an adequate pump function in the presence of ventricular dysfunction. As already pointed out, a partial agonist should also buffer the myocardium from potentially harmful decreases or increases in sympathetic tone, as may occur during sleep or exercise, respectively.

om such stabilization of the inotropic state.

Patients with CAD and significant LV dysfunction ight perhaps be among the best indicators of such artial agonists. Many patients with MI cannot receive eta-blocking agents, and it was recently suggested that igitalis could also be detrimental in this setting.[5] Accordingly, a partial agonist, which is able to antagonize xcessive sympathetic stimulation[7,9,23] and at the same me prevent myocardial depression and inappropriate radycardia, might open interesting therapeutic perpectives. Similarly, in other forms of heart failure with oderately elevated cardiac filling pressures at rest, a artial agonist appears to improve resting hemodyamic function and exercise tolerance.[29] In such cases, partial agonist could also prevent the frequent exacbations of pulmonary congestion during the night hich not only are related to the supine position but also ay be caused by the decreased sympathetic drive uring sleep.[30] Further studies are needed to evaluate e effects of such agents on functional capacity and to etermine whether changes in $beta_1$ adrenoceptor umber or sensitivity might occur after their prolonged dministration, resulting in tachyphylaxis.

In conclusion, in patients with CAD and ventricular ysfunction, corwin improves cardiac function and efciency without inducing myocardial ischemia. herefore, considering its lack of arrhythmogenic acvity[23] and its property to antagonize deleterious effects f high levels of circulating catecholamines,[7,9,23,29] rwin represents a promising inotropic drug in the ifficult setting of ischemic heart disease.

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Relation of Segmental Wall Motion to Global Left Ventricular Function in Acute Myocardial Infarction

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The relation of left ventricular regional wall motion to global ventricular function was evaluated by radionuclide ventriculography in 127 patients within 18 hours of acute myocardial infarction. No patient had evidence of previous myocardial infarction. The following parameters were measured: (1) wall motion index; (2) percent of abnormally contracting segment; (3) ejection fraction (EF); (4) end-diastolic volume (EDV) and end-systolic volume (ESV); and (5) peak systolic cuff pressure/end-systolic volume ratio (PSP/ESV). The measurements of global function correlated well with wall motion index ($r = 0.83$, $p < 0.001$ for EF; $r = -0.69$, $p < 0.001$ for ESV; and $r = 0.061$, $p < 0.001$ for PSP/ESV), but EDV correlated less well ($r = -0.35$, $p < 0.001$). Multiple linear regression analysis revealed that EF correlated best with wall motion index, and no other parameters of global left ventricular function added significantly to the regression.

The correlation of motion in each segment with EF was determined by multiple linear regression analysis. Ejection fraction correlated best with motion in the anterobasal, then in order of correlation, in the apical-septal, inferoapical, anterolateral, and superlateral walls. The relation of EDV, ESV, and degree of percent abnormally contracting segments was as follows: EDV did not increase with a mild regional wall motion abnormality; however, ESV did increase and reduced stroke volume. As percent abnormally contracting segments worsened, enlargement of both EDV and ESV was seen and was associated with further reduction in systolic volume.

These data suggest that EF is the best global left ventricular function correlate of the severity of the regional wall motion abnormality, and that abnormal motion in the territory of the left anterior descending coronary best predicts reduction in global left ventricular function. Radionuclide ventriculography is useful in characterizing global and regional left ventricular function in the early hours of acute myocardial infarction.

Impairment of left ventricular function in acute myocardial infarction has been directly related to the quantity of myocardium damaged.[1–6] The size of the acute infarct, as determined by enzymatic, electrocardiographic, and angiographic approaches, has been shown to correlate with ejection fraction (EF).[7,8] Furthermore, in patients with acute myocardial infarction, EF correlates well with clinical and hemodynamic evidence of heart failure.[9] Recent studies suggest that other parameters of global left ventricular function such as end-diastolic and end-systolic volumes may offer additional insights into left ventricular function, because the EF may be affected by factors other than contractility such as left ventricular afterload or preload, or both.[10–12] The left ventricular pressure/volume ratio at end-systole has been suggested as a valuable parameter for assessing global function because it appears to be relatively insensitive to cardiac loading and reflects changes in left ventricular contractility.[13] In addition, although the effect of location and type of asynergy on the ejection and nonejection phase indexes has been

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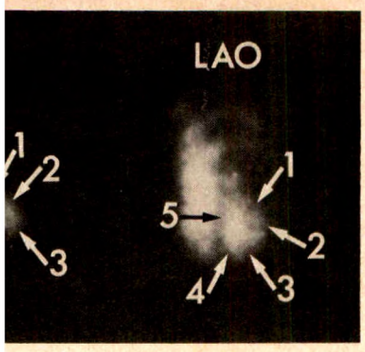

e ventriculographic images demonstrating an-
eral (2), apical (3), diaphragmatic (4), and in-
nterior (ANT) projection, and basal-septal (5),
apical (3), posterolateral (2), and superolateral
anterior oblique (LAO) projection.

with myocardial infarction at diag-
tion,[14] the studies were rarely per-
hours of myocardial infarction and
the end-systolic pressure/volume

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thin 18 hours of the onset of acute
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h parameter of global left ventricular
s closest with the severity of the re-
abnormality (infarct size)? Is there
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bal left ventricular function?

Methods

on: Radionuclide ventriculography was
dside in 127 patients within 18 hours of
yocardial infarction. The mean age was
lard deviation) with a range of 21 to 76.
farction was diagnosed using the criteria
ticenter Investigation of the Limitation
[S) trial: at least 2 of the following 3 were
of typical prolonged chest pain; (2) de-
ogic Q waves 0.04 second in duration in
diographic leads; and (3) characteristic
rum enzymes (creatine kinase, glutamic
ase, and lactic dehydrogenase). Patients
y had (1) cardiogenic shock or required
blood pressure, (2) cardiomyopathy, or
ers. No patient was receiving either dig-
at the time of radionuclide ventriculog-

re obtained for creatine phosphokinase
admission and every 6 hours thereafter
ate was measured from the electrocardi-
ng radionuclide ventriculography. Sys-
was recorded using a cuff sphygmoma-
ging.[15]

ntriculography[16,17]: The patient's red
eled in vivo by administering 3 mg of
hate (Pyrolite, New England Nuclear,
ssachusetts) intravenously followed 20
nCi of technetium-99m pertechnetate.
pool images were recorded in both the anterior and 45° left anterior oblique projection which best defined the ventricular septum with an Anger scintillation camera (Ohio-Nuclear Series 420 mobile camera with 550 computer) equipped with an all-purpose, parallel-hole collimator. The pulse height analyzer was centered at 140 keV with a 20% window. The cardiac cycle was separated into ≥20 equal segments. A minimum of 200,000 counts were collected in each segment.

To calibrate the images for calculation of volume, a lead bar pattern of known dimensions was imaged at the conclusion of patient data collection. The number of picture elements between the bars on the image was determined and compared with the distance between the bars to complete the calibration process.

The data were translated and interpreted in a standardized fashion on a Medical Data System (MDS) A^2 computer. The data were reviewed and interpreted independently by at least 2 experienced observers, and the results were averaged.

Radionuclide data analysis: The left ventricular EF was calculated from the left anterior oblique view using a variable region of interest-counts method. Previous studies in our laboratory have revealed <5% intraobserver variance with this method.[17]

The end-diastolic volume (EDV) was calculated using a biplane area-length method.[18,19] Briefly, after calibration of picture element size, the end-diastolic outline of the ventricle was drawn by the viewer in both the anterior and left anterior oblique views, and then longest chords, areas, and minor axes were determined and corrected for nonorthoganality and rotation by computer and the end-diastolic volume was calculated. To validate the determination of EDV with the area-length method, the radionuclide EDV was correlated with that derived from direct contrast angiography in 44 other patients having both studies within 2 weeks,[20] with an overall correlation coefficient of $r = 0.84$. The stroke volume and end-systolic volume (ESV) were calculated from the EF and EDV. The peak systolic cuff pressure/end systolic volume ratio (PSP/ESV) was calculated from the cuff systolic pressure as has previously been reported.[19] Cardiac output was calculated as stroke volume times heart rate. Volumes were expressed as both absolute volume and corrected for body surface area.

To define regional wall motion, the left ventricular perimeter was divided into 5 segments on the anterior and left anterior oblique views (Fig. 1) as defined in the Coronary Artery Surgery Study Protocol.[21] A 5-point grading scale, ranging from 4 (normal) to 0 (dyskinesis), was assigned to each segment by 2 observers viewing an endless-loop movie of the multigated scan in both the anterior and left anterior oblique projections.[17] The score of each segment was summed to derive a wall motion index. Therefore, 40 (10×4) was the highest possible (normal) wall motion index score. Patients then were divided into 5 groups, ranging from near normal to severely impaired, based on their wall motion index: Group 1 = 36 to 40; Group 2 = 31 to 35; Group 3 = 26 to 30; Group 4 = 21 to 25; Group 5 ≤20. In addition, the percent abnormally contracting segments (that is, segments that were akinetic or dyskinetic—percent abnormally contracting segments) was calculated. The percent abnormally contracting segments was expressed in multiples of 10%, because the left ventricular perimeter was divided into 10 segments.

Statistical analysis: Mean differences among groups of patients were analyzed by means of a one-way analysis of variance and the Neuman-Keuls multiple comparison test. The correlation between parameters was assessed using linear regression analysis.[22] Differences of these correlations were assessed by Fisher's Z value. To determine which of these parameters of global left ventricular function correlated best

TABLE I Parameters of Left Ventricular Function in Acute Myocardial Infarction

	Wall Motion Index Groups				
	I: 36–40 (n = 25)	II: 31–35 (n = 12)	III: 26–30 (n = 34)	IV: 21–25 (n = 28)	V: ≤20 (n = 28)
%ACS	0.4 ± 2.0	5.8 ± 6.7	14.4 ± 11.3	31.4 ± 12.1	48.6 ± 16.3
HR	81 ± 18	71 ± 14	74 ± 10	86 ± 20	91 ± 14
PSP (mm Hg)	143 ± 29	142 ± 28	136 ± 27	139 ± 23	132 ± 23
EDVI (ml/m^2)	69 ± 18	63 ± 15	77 ± 21	86 ± 22	88 ± 28
ESVI (ml/m^2)	23 ± 11	29 ± 8	38 ± 14	52 ± 17	63 ± 25
SVI (ml/m^2)	46 ± 11	34 ± 9	39 ± 12	34 ± 12	25 ± 8
CI (liters/min/m^2)	3.7 ± 0.9	2.5 ± 0.9	3.4 ± 1.0	3.0 ± 0.9	2.1 ± 0.7
EF (%)	68 ± 10	55 ± 6	51 ± 10	40 ± 10	30 ± 11
PSP/ESV (mm Hg/ml)	4.5 ± 2.4	2.8 ± 1.0	2.3 ± 1.2	1.6 ± 0.6	1.3 ± 0.8

Global left ventricular function in relation to wall motion index. Results are expressed as the mean ± 1 standard deviation. Differences betwee groups were analyzed by 1-way analysis of variance and the Newman-Keuls multiple comparison test.

* $p < 0.05$.

† $p < 0.01$.

%ACS = the percentage of abnormally contracting segments; CI = cardiac index; EDVI = left ventricular end-diastolic volume index; EF = ejection fraction; ESVI = left ventricular end-systolic volume index; HR = heart rate; PSP = peak systolic blood pressure; PSP/ESV = peak systoli blood pressure/left ventricular end-systolic volume; SVI = stroke volume index.

with wall motion index and which segment score correlated with global left ventricular function, a stepwise multiple linear regression analysis was employed. In this analysis, each segment score was evaluated for its ability to explain the variation in global ventricular response. Those segments whose scores correlated best with global function were identified, and the analysis was repeated with exclusion of these data to identify the next most important segment, and so forth. Differences in the incidence of abnormal wall motion in each segment were assessed by the chi-square test. All mean values were expressed as mean ± 1 standard deviation.

The peak CPK value was compared with the EF at the time of admission by linear regression analysis.

Results

Relation of global left ventricular function and wall motion index (Table I): Increasingly severe wall motion abnormalities were associated with significant increases in heart rate and ESV, whereas EDV began to increase only after more severe damage to the myocardium (Groups IV and V). There were significant decreases in EF, stroke volume, cardiac index, and PSP/ESV with moderate reduction in wall motion (Group II). Peak systolic cuff pressure was not significantly different among the groups. Eleven patients had completely normal wall motion (index of 40) and their mean global function values were: EF 72 ± 10%; EDV 70 ± 11 ml/m^2; ESV 201 ± 11 ml/m^2; and PSP/ESV 5.(± 2.3 mm Hg/ml. These values do not differ signifi cantly from those of the Group I patients and did no differ from normal values previously reported from ou laboratory.[18,19]

The parameters of global left ventricular functio whose correlation coefficients reached statistical sig

TABLE II Correlation Coefficients Between Parameters of Global Left Ventricular Function and 2 Parameters of Segmental Wall Motion

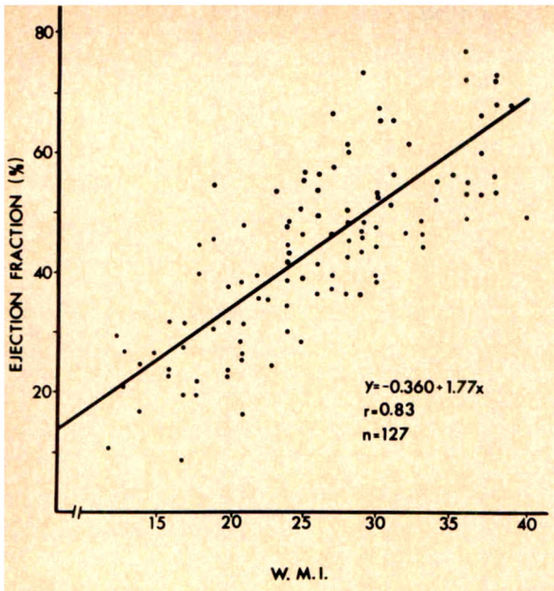
	WMI		%ACS		p
Ejection fraction	0.83	*	−0.66		<0.001
End-systolic volume-diastolic	−0.69		0.54	†	<0.01
Peak systolic blood pressure/ left ventricular end-systolic volume	0.61	†	−0.44		<0.01
Stroke volume index	0.55		−0.47	*	NS
Cardiac index	0.49	‡	−0.41		NS
End-diastolic volume-diastolic	−0.35		0.25		NS

Linear regression analysis of global left ventricular function with wal motion index (WMI) and % abnormally contracting segments (%ACS) Differences between correlation coefficients were assessed by Fisher's z value.

* $p < 0.001$.

† $p < 0.05$.

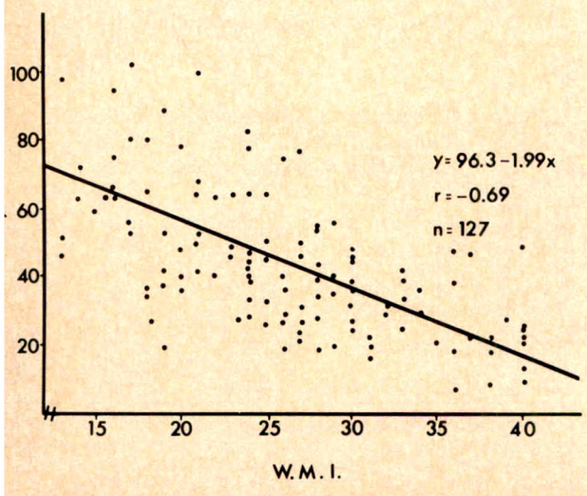
‡ $p < 0.01$.



URE 2. Relation of left ventricular ejection fraction to wall motion ex (W.M.I.). The line of best fit is plotted and the regression equation hown along with the correlation coefficient.

icance when compared with wall motion index are own in Table II. The correlation coefficient for EF th wall motion index was significantly larger than the lues for PSP/ESV and ESV with wall motion index. roke volume and cardiac index correlated less well th wall motion index and EDV correlated poorly with ll motion index. The individual plots for EF, ESV, d PSP/ESV in relation to wall motion index are own in Figures 2 to 4.

Stepwise multilinear regression of parameters of bal left ventricular function with wall motion index vealed that EF was the best correlate (F = 96.0, p .001), explaining 73% of the variance of regression:



URE 4. Relation of left ventricular end-systolic volume index (ESVI) wall motion index (W.M.I.).

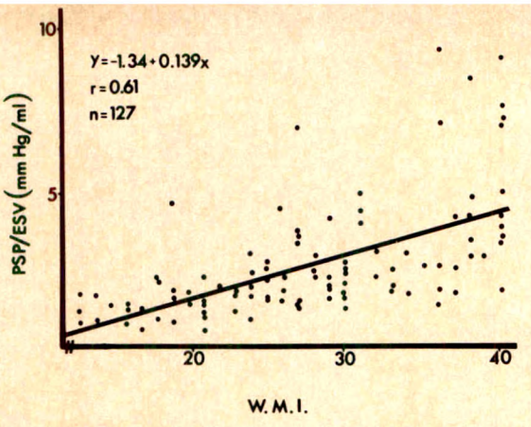


FIGURE 3. Relation of peak systolic blood pressure/left ventricular end-systolic volume (PSP/ESV) to wall motion index (W.M.I.).

wall motion index = 8.879 + 36.0 × EF. No other parameter added significantly to the regression.

Relation between EF and PSP/ESV: The relation between EF and PSP/ESV was curvilinear (Fig. 5). This basis relation was not altered when ESV was normalized by body surface area. When EF was related to the log of PSP/ESV, a significant linear correlation was found; log PSP/ESV = 0.458 (−0.0308 × EF) (r = 0.83, p <0.00005) (Fig. 6).

Influence of regional wall motion on global left ventricular function: The incidence of abnormal wall motion in each segment is shown in Table III. The apical and inferoapical segments were most frequently involved, whereas the anterobasal and superolateral segments were least frequently involved. All segments were involved in at least 30% of the patients. The anterobasal, superolateral, or inferobasal segments were not abnormal unless another segment was also involved. In 47 patients in which these 3 segments were normal, the percent abnormally contracting segments was sig-

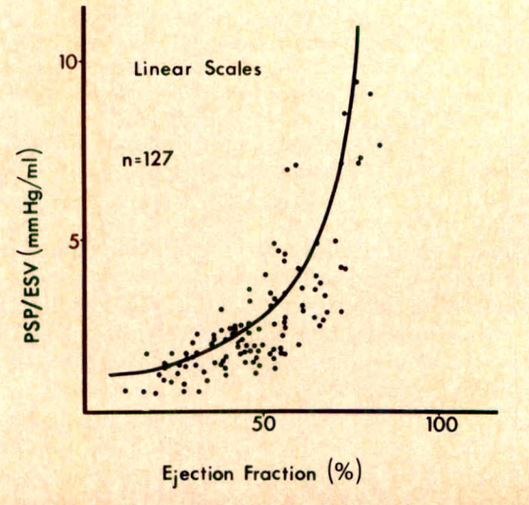


FIGURE 5. Relation between peak systolic blood pressure/left ventricular end-systolic volume (PSP/ESV) and ejection fraction.

nificantly smaller than in the 69 cases in which the aforementioned segments were abnormal (18 ± 16% and 29 ± 22%, p <0.005).

The correlations of EF, PSP/ ESV, and ESV with regional wall motion scores by multiple linear regression analysis are shown in Table IV. Motion in the apical-septal, anterobasal, inferoapical, anterolateral, and superolateral walls correlated best with EF; EF = −15.35 + 7.38 × (anterobasal) + 3.36 × (apical-septal) + 3.32 × (inferoapical) + 2.95 × (anterolateral) + 3.95 × (superolateral) where EF is in percent units. These segments also correlated best with both ESV and PSP/ESV.

The peak CPK values ranged from 76 to 2,050 IU and correlated poorly with EF (r = 0.17).

Discussion

Radionuclide method of assessing left ventricular function: Previous studies from several laboratories[23–26] have demonstrated that radionuclide techniques correlate closely with contrast ventriculography in measuring EF and regional wall motion. Recent work by Boucher et al[18] and Massie et al[27] shows that the determination of left ventricular EDV using the geometric method employed in this study correlates well with that derived from contrast angiography. In addition, Palacios et al[28] correlated left ventricular volume calculated from biplane gated scan using the area-length method with the true volume in human cadaver hearts and found a close correlation (r = 0.98). To minimize any potential problems with the assumed geometric ellipsoid model, the volume was calculated on the end-diastolic image only and ESV derived from EDV and EF.

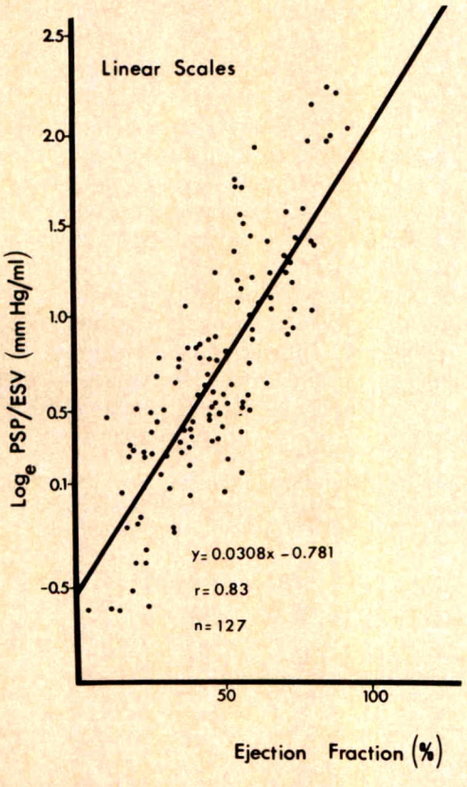


FIGURE 6. Relation between peak systolic blood pressure/end-systolic volume (PSP/ESV) and ejection fraction. The values in PSP/ESV were transformed into natural logarithmic number, and linear regression analysis between PSP/ESV and ejection fraction was performed.

TABLE III Frequency of Abnormal Wall Motion in Each Left Ventricular Segment (n = 127)

Anterior view		
Anterobasal	41	32%
Anterolateral	92	72%
Apical	108	85%
Diaphragmatic	93	73%
Inferobasal	55	43%
Left anterior oblique view		
Basal-septal	89	70%
Apical-septal	95	75%
Inferoapical	107	84%
Posterolateral	82	65%
Superolateral	39	31%

The use of PSP/ESV as a noninvasive measure of contractility has been reported,[19,29,30] but makes the following assumptions: (1) the left ventricular end-systolic pressure-volume relation is linear; (2) the intercept of the line of end-systolic pressure volume relation does not change significantly with the early stage of acute myocardial infarction; (3) left ventricular end-systolic pressure can be approximated by the systolic pressure measured by the cuff method; and (4) left ventricular ESV may be assessed noninvasively.

Previous studies have correlated regional wall motion scores for the gated scan within ±1 grade with scores for contrast ventriculography in 84% of patients. This correlation was observed despite the fact that the inferobasal segment of the left ventricle may be difficult to define on the anterior view, and the wall motion analyzed for the septum differs in the 2 technologies. The best agreement occurred in the anterolateral surface (88%), and the worst agreement in the apex and septum (82%).[17,26,31] Although quantitative methods employing either a count-based or geometric analysis were avail-

TABLE IV Stepwise Multiple Regression Analysis of Segmental Wall Motion with EF, PSP/ESV, and ESV

	EF (%)	PSP/ESV	ESV (ml/m^2)
Anterobasal	17.8*	7.1‡	42.7†
Anterolateral	6.0*	NS	NS
Apical	NS	NS	10.1†
Diaphragmatic	NS	NS	NS
Inferobasal	NS	NS	NS
Basal-septal	NS	NS	NS
Apical-septal	19.5*	7.2†	9.8†
Inferoapical	13.3*	16.4*	NS
Posterolateral	NS	NS	NS
Superolateral	5.1‡	NS	NS
Percent variation explained	71	35	51

* Significant F value (p <0.001).
† Significant F value (p <0.01).
‡ Significant F value (p <0.05).
EF = ejection fraction; ESV = end-systolic volume; NS = not significant; PSP/ESV = peak systolic pressure/end-systolic volume.

ible for determination of regional wall motion, they were not employed in this study. Instead, the subjective method of interpretation using multiple independent readers as just described was used.

Relation of global left ventricular function to wall motion index: Ejection fraction, PSP/ESV, and ESV were abnormal even in patients (Group II) with relatively mild reduction in wall motion. The acute response to a small or moderate-sized myocardial infarction was an increase in ESV and a decrease in stroke volume without a significant change in EDV. Only in patients with severe impairment of wall motion did the EDV increase, as ESV increased in excess of the decrease in stroke volume. Our data are consistent with those of Klein et al[32] who found that the left ventricle only enlarges when 20 to 25% of the surface area is rendered akinetic.

Twenty-five patients (20%) had a small enough infarct that their wall motion was nearly normal (Group), and 11 (9%) had completely normal regional wall motion and global left ventricular function. The explanation for the lack of sensitivity of radionuclide ventriculography for a small infarct is unclear. The parameters measured in these patients may possibly have worsened compared with their preinfarct status, but were still in the normal range. It is less likely that an increase in contraction of the noninfarcted area may have occurred (because of increased sympathoadrenal discharge)[33,34] to maintain global function, because no abnormality in regional function was observed.

Although EF, ESV, and PSP/ESV correlated well with wall motion index, a stepwise multilinear regression analysis revealed that EF was the best single correlate and that no other variable added significantly to the regression. These data suggest that within hours of the acute injury, EF is the best indicator of overall wall motion in the early phase of acute myocardial infarction.

Previous studies have demonstrated that ESV increased when left ventricular contractility was reduced and when afterload was increased but was minimally affected by isolated changes in preload.[35–37] As a result, some suggest that ESV is a better indicator of intrinsic myocardial function than is the EF.[38] Although ESV did increase as wall motion worsened, this parameter did not correlate with wall motion as well as did EF. However, information about ventricular volumes and systolic blood pressure might be of additional value to EF for a more complete understanding of the changes in the functional state of the left ventricle.

The relation between PSP and ESV (PSP/ESV) is an attempt to make a noninvasive approximation of contractility (Emax), a parameter of left ventricular function that appears to be independent of preload which incorporates afterload.[39] A decrease in Emax has been found in patients with low EF.[12,40] Furthermore, previous studies suggested that it may be useful in detecting subtle abnormalities of left ventricular function in coronary disease.[29,30] However, our data suggest that in patients with acute myocardial infarction its value in addition to EF is less certain.

The nonlinear relation between PSP/ESV and EF (Fig. 5) is similar to that of Sagawa et al[13] concerning Emax and EF. The shape of the curve suggests an insensitivity of the normal EF to changes in Emax, whereas there is an insensitivity of the reduced Emax to changes in EF. This finding is not surprising because these parameters are derived from each other. The PSP/ESV was derived from PSP/(EDV × (1 − EF)). Because PSP was not significantly different between groups, the PSP/ESV ratio might be approximately expressed as constant/1 − EF.

Contribution of segmental wall motion to global function: Although Herman and Gorlin[14] and other investigators[41–43] have examined the relation of the location of Q wave to asynergy in left ventricular ventriculograms, postmortem infarct size, or coronary artery anatomy, or all 3, the relation of segmental wall motion to global ventricular function in the early phase of patients with myocardial infarction has not been examined in detail. In the present study the percent abnormally contracting segments of the walls usually perfused by the left anterior descending coronary artery (apical-septal, anterobasal, inferoapical, anterolateral and superolateral) correlated with EF. Although the anterobasal and superolateral walls were abnormal the least frequently, these segments appear to be involved in patients with larger infarctions.

Of interest, we found no correlation between peak creatine kinase and EF. One explanation is that a variable degree of ischemic dysfunction (reduced wall motion in noninfarcted areas) may have been present in our patients, a finding consistent with the observation that EF improves in some patients after infarction. In addition, the selection of patients for these studies eliminated those with extensive necrosis and cardiogenic shock, thereby limiting the range of comparisons between the 2 parameters. Alternatively, peak creatine kinase may not be an ideal measure of infarct size, and an integration of the area under the creatine kinase curve may be better. In either case, this lack of correlation does not alter the basic observations of the study regarding the relation of global to regional function in acute myocardial infarction; moreover, in the acute situation, in a patient with a first infarction, EF characterizes left ventricular function better than any other parameter.

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Effect of Metoprolol on Indirect Signs of the Size And Severity of Acute Myocardial Infarction

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In a double-blind randomized trial, 1,395 patients with suspected acute myocardial infarction (MI) were investigated to evaluate the possibility of limiting indirect signs of the size and severity of acute MI with the beta$_1$-selective adrenoceptor antagonist metoprolol. Metoprolol (15 mg) was given intravenously and followed by oral administration for 3 months (200 mg daily). Placebo was given in the same way. The size of the MI was estimated by heat-stable lactate dehydrogenase (LD[EC 1.1.1.27]) analyses and precordial electrocardiographic mapping. Lower maximal enzyme activities compared with placebo were seen in the metoprolol group (11.1 ± 0.5 μkat·liter^{-1}) when the patient was treated within 12 hours of the onset of pain (13.3 ± 0.6 μkat·liter^{-1}; n = 936; p = 0.009). When treatment was started later than 12 hours, no difference was found between the 2 groups. Enzyme analyses were performed in all but 20 patients (n = 1,375). Precordial mapping with 24 chest electrodes was performed in patients with anterior wall MI. The final total R-wave amplitude was higher and the final total Q-wave amplitude lower in the metoprolol group than in the placebo group. Patients treated with metoprolol ≤12 hours also showed a decreased need for furosemide, a shortened hospital stay, and a significantly reduced 1-year mortality compared with the placebo group, whereas no difference was observed among patients treated later on. After 3 months, however, there was a similar reduction in mortality among patients in whom therapy was started ≤12 hours and >12 hours after the onset of pain. The results support the hypothesis that intravenous metoprolol followed by oral treatment early in the course of suspected myocardial infarction can limit infarct size and improve long-term prognosis.

The conventional treatment of patients with acute myocardial infarction (MI) is directed mainly at complications such as pump failure and arrhythmias. An alternative approach is to attempt to influence the natural evolution of the impending MI by interrupting the process in its reversible phase, thereby limiting the final size of the MI.

The size of the MI greatly influences the short-term prognosis[1] and most likely also the long-term prognosis.[2] The hypothesis that beta blockade may limit MI development in man emanates from animal studies,[3–5] which were followed by several pilot investigations in man.[6–8] In most studies, results indicating MI limitation were obtained. However, the number of patients was mostly small and a placebo group was not always included. In a previous report, results regarding overall mortality in the metoprolol study were presented. A secondary objective of this trial was to investigate whether the beta$_1$-selective adrenoceptor antagonist metoprolol given intravenously and orally in the acute stage of suspected MI limits indirect signs of the size and severity of acute MI.

Methods

Between June 1976 and January 1981 all patients entering the 2 coronary care units in the city of Göteborg and that in the nearby community hospital in Skövde were assessed. Criteria for inclusion in the study were (1) residence in the recruitment area, (2) chest pain of acute onset and ≥30 minutes' duration or electrocardiographic signs of acute MI with estimated onset of MI within the previous 48 hours, (3) age between 40 and 74 years. The entry criteria were fulfilled by 2,619 patients, who were then evaluated with regard to possible exclusion (Table I). A detailed description of the study design and of the 3-month mortality was given previously.[9] After exclusion, 1,395 patients were randomly allocated to

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TABLE I Selection of Patients for the Study

Selection	Number (%)
Patients eligible for the study	2,802
Patients included in other studies	183
Patients evaluated for entry	2,619
Patients excluded from entry because of contraindications	1,224 (47)*
Contraindications to beta blockade	353 (28)
Cardiovascular	311 (25)
Hypotension (<100 mm Hg)	63 (5)
Bradycardia (<45 beats/min)	21 (2)
Heart failure (basal rales <10 cm, poor peripheral circulation, shock)	183 (15)
Atrioventricular block	44 (3)
Bronchial asthma	42 (3)
In need of beta blockade	257 (21)
Serious or multiple diseases	92 (8)
Administrative reasons	510 (42)
Refusal to participate	131 (11)
Psychiatric disease, alcoholism	126 (10)
Chronic atrial fibrillation	67 (5)
Pacemaker at entry	43 (4)
Nonresident or language problems	43 (4)
Planned or previous coronary bypass	38 (3)
Minor noncardiovascular adverse reactions to beta-blockade	27 (2)
Confused or unconscious	20 (2)
On "CA^{++} antagonists" at entry	15 (1)
Reason missing	12 (1)
Randomized to blind treatment	1,395 (53)*

* The percentage of 2,619 patients is given for the number of patients excluded because of contraindications and those randomized, respectively. All other figures in parentheses represent the percentage of patients who were excluded from entry.

TABLE II Patient Profile: Comparison of Placebo and Metoprolol Groups

Characteristics	Placebo Group (n = 697) (%)	Metoprolol Group (n = 698) (%)
Sex		
Men	76.2	75.5
Women	23.8	24.4
Age (yr)		
<64	65.0	66.5
65–74	35.0	33.5
Clinical history		
Previous infarction	22.7	21.2
Angina pectoris (5)*	34.7	35.7
Hypertension	29.7	29.1
Therapy before admission		
Digitalis (6)	12.9	12.5
Diuretics (5)	18.7	18.7
Beta-blocking drugs	25.4	25.2
Clinical status at entry		
Pulmonary rales	9.0	11.6
ECG signs of infarction (1)	47.8	49.9
Heart-rate >100 beats/min (1)	6.2	4.7
Systolic blood-pressure <110 mm Hg (2)	4.4	3.3
Dyspnea at onset of pain (29)	30.8	28.8
Treatment in hospital before blind injection		
Morphine (3)	53.9	53.6
Atropine (3)	3.5	2.9
Isoprenaline or analogues (2)	0.0	0.0
Diuretics (3)	9.8	10.8
Digitalis (3)	1.9	2.3
Lidocaine (3)	2.7	2.3
Beta-blocking drug or verapamil (5)	1.6	2.2
Mean age ± SEM	60.0 ± 0.3	60.0 ± 0.3
Mean time from onset of symptoms to blind injection ± SEM (16)	11.4 ± 0.4	11.1 ± 0.4

* Numbers of missing data are given in parentheses.
SEM = standard error of the mean.

double-blind treatment; 698 received metoprolol and 697 placebo. Patient characteristics are given in Table II.

Treatment was started as soon as possible after arrival in the hospital. Metoprolol was given in a dose of 15 mg intravenously (5 mg at a time with 2-minute intervals between injections) followed by 50 mg orally every 6 hours (first tablet 15 minutes after last injection) for 48 hours and then 100 mg twice a day for 3 months. Placebo was given in the same way. After 3 months, patients with ischemic heart disease and no contraindications were treated with metoprolol 100 mg twice daily for at least 2 years. The distribution of patients in relation to the time interval between onset of pain and blind injection is given in Figure 1. In patients included in the study developing a systolic blood pressure <90 mm Hg, heart rate <40 beats/min, atrioventricular block (P-Q ≥0.26 second), or severe heart failure, the dose was usually halved. If no improvement occurred, the blind medicine had to be withdrawn (Table III).

Blood samples for heat-stable lactate dehydrogenase (LD [EC 1.1.1.27] earlier referred to as LD I + II[9]) analysis were taken every 12 hours for 48 hours in 466 patients, for 60 to 84 hours in 191 patients, and for 96 to 108 hours in 718 patients. Heat-stable LD values were thus obtained in all but 20 patients (n = 1,375). In the remaining 20 patients either samples were lost or it was impossible to obtain blood from the patient because of poor clinical condition, early death, or unwillingness. The highest enzyme value obtained in each patient was used as a measure of the infarct size. To correlate this enzyme with a more widely used enzyme, creatine kinase (CK [EC 2.7.3.2]) and also CK B was analyzed every 6 hours for 48 hours in a subgroup. The heat-labile isoenzymes of LD were inactivated according to the method described by Brydon and Smith.[10] LD, aspartate amino transferase (ASAT), and alanine amino transferase (ALAT) were determined according

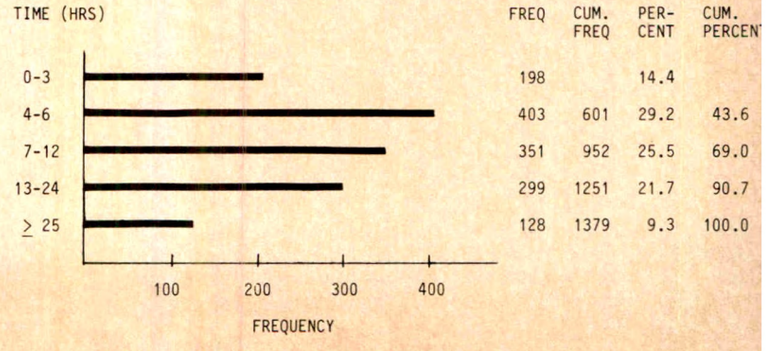

FIGURE 1. Number and percentage of patients given blind injections within different time intervals after onset of pain. Missing data in 16 patients. CUM. = cumulative; FREQ = frequency.

Cardiovascular Reasons During the Initial Hospital Stay

Reasons for Withdrawal	Patients Withdrawn: Placebo Group (696) n	Placebo Group (696) %	Metoprolol Group (696) n	Metoprolol Group (696) %	Significance (2p)
Hypotension	10	1.4	26	3.7	0.010
Bradycardia	5	0.7	16	2.3	0.026
Atrioventricular block II or III	10	1.4	15	2.2	>0.2
Heart failure	3	0.4	3	0.4	...
Need for beta-blockade	13	1.9	6	0.9	0.160
Total	41	5.9	66	9.5	0.012

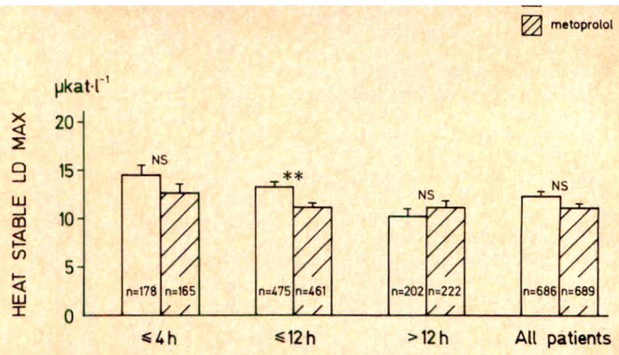

FIGURE 2. Mean maximal (MAX) heat-stable lactate dehydrogenase (LD) activities in all patients and those given blind injection within different time intervals after the onset of pain. Missing data in 15 of the patients in whom enzyme values were obtained. ** $p < 0.01$.

to the method recommended by the Scandinavian Committee on Enzymes.[11] CK was determined according to a modified method recommended by the Scandinavian Committee on Enzymes.[12]

CK B was determined with an immune inhibition method according to Gerhardt and Waldenström.[13] The area under the enzyme curve was calculated according to Davis and Rabinowitz.[14] One enzyme unit catal is defined as the enzyme activity that transforms 1 mole of substrate per second.

Precordial mapping with 24 chest electrodes arranged in 6 vertical rows (the first 2 rows symmetrically on both sides of the sternum) was performed before the blind injection and 4 days later. The Q and R wave amplitude was analyzed in patients with anterior MI (changes in leads V_1 to V_5 in standard electrocardiogram). A pathologic Q wave was defined as >0.03 second wide and >1 mm deep or ≥0.03 second wide with a Q/R ratio ≥0.33 and >1 mm deep. The paper speed was 50 mm/s. Amplification was standardized, that is, 10 mm = 1 mV.

A QRS duration >0.10 second or axis deviation beyond −30° and +120° in the frontal plane was not accepted. The P-Q segment was used as the isoelectric line. Mapping was performed at end-expiration and reclining at 30°. At each electrocardiographic position the Q and R waves were measured to the nearest 1.0 mm. The total R-wave amplitude (ΣR) and total Q-wave amplitude (ΣQ) in the 24 electrodes were calculated on the fourth day.

The following criteria were used for classification of definite and probable MI. For definite MI 2 of the following 3 criteria had to be fulfilled: (1) chest pain of at least 15 minutes' duration, (2) Q-wave or S-T segment elevation followed by T-wave inversion in at least 2 electrodes in a 12-lead standard electrocardiogram, and (3) 2 serum ASAT values above the normal value in combination with lower or normal serum ALAT values. Electrocardiographic changes in only 1 electrode or only 1 elevated ASAT value in combination with at least 1 heat-stable LD value above a discriminatory level were also regarded as definite MI. For probable MI, chest pain plus 1 of the following criteria was required: (1) T-wave inversions, (2) 1 elevated ASAT value in combination with lower or normal ALAT values, (3) 1 or more elevated heat-stable LD values, or (4) Q-wave or S-T segment elevation followed by T-wave inversion in only 1 electrode.

Late infarction was defined according to chest pain, ASAT, and electrocardiographic changes (in the same manner as previously described) or autopsy findings of an actual infarction that could be separated from a suspected initial infarction. The start of new symptoms related to the infarction must occur >3 days after inclusion in the study. Blood samples for heat-stable LD were not analyzed in these cases.

The total dose of furosemide given during the first 4 days in the hospital was calculated in 79% of the patients. The re-

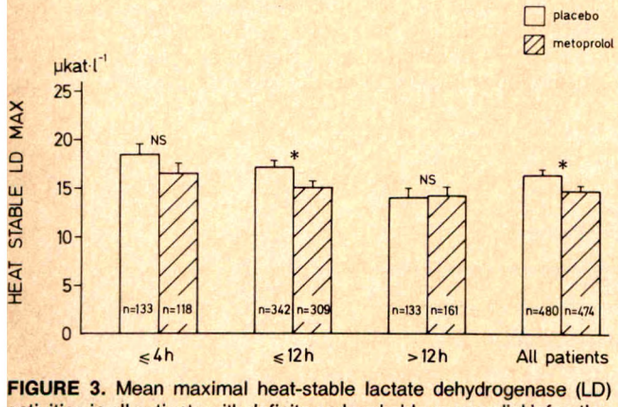

FIGURE 3. Mean maximal heat-stable lactate dehydrogenase (LD) activities in all patients with definite and probable myocardial infarction and those given blind injection within different time intervals after the onset of pain. Missing data in 9 patients in whom enzyme values were obtained. * $p < 0.05$.

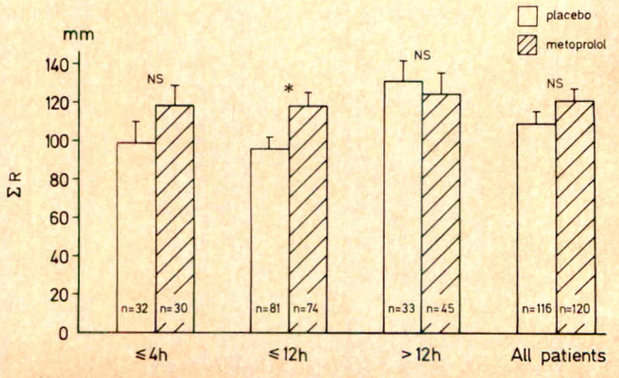

FIGURE 4. The sum of all R waves in the 24 precordial positions on the fourth day in anterior myocardial infarction (MI). * $p < 0.05$.

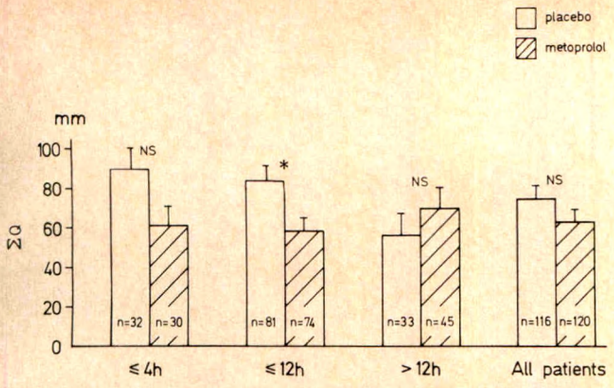

FIGURE 5. Sum of all Q waves in the 24 precordial positions on the fourth day of anterior myocardial infarction (MI). * p <0.05.

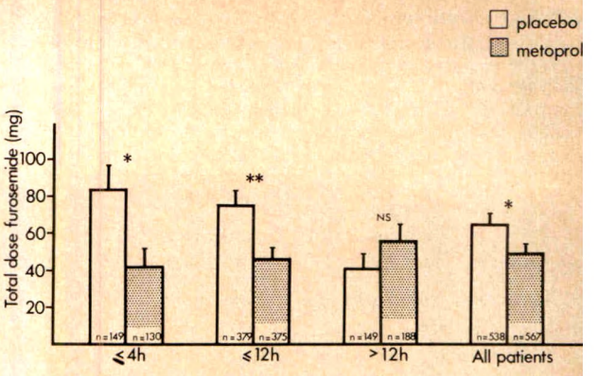

FIGURE 6. The total dose of furosemide given during the first 4 da in hospital. * p <0.05; ** p <0.01.

maining 21% in whom data were not collected included (1) patients on chronic furosemide before inclusion receiving furosemide after inclusion, and (2) patients receiving additional diuretics other than spironolactone. In a subgroup analysis regarding time from the onset of pain to the start of treatment, 4 and 12 hours were used as time limits. The reason was that in previous reports, which will be referred to, these time limits were used. All analyses presented are in accordance with the "intention to treat" concept.

Statistical methods: Fisher's permutation test was used.[15] A 2-tailed test was applied and a p value <0.05 was considered significant. Results are expressed as mean values ± standard error of the mean (SEM).

Results

Enzymes: *All patients* (*Fig. 2*): When all randomized patients were included, slightly lower activity (borderline significance) was found in the metoprolol group (11.1 ± 0.4 μkat·liter^{-1}) compared with the placebo group (12.4 ± 0.5 μkat·liter^{-1}; n = 1,375; p = 0.054). A highly significant difference in the total series was found in the patients treated within 12 hours of onset of pain (metoprolol 11.1 ± 0.5 μkat·liter^{-1}; placebo 13.3 ± 0.6 μkat·liter^{-1}; n = 936; p = 0.009). If treatment was started later than 12 hours after onset of pain, no difference between treated and untreated patients was observed. The disappearance rate of heat-stable LD was similar in the 2 groups. Altogether, a definite infarction developed in 399 patients during the first 3 days in the metoprolol group compared with 410 patients in the placebo group (difference not significant [NS]). Among patients included after ≤12 hours, the number of patients in respective groups in whom an infarction developed were as follows: metoprolol, 256 of 468 (55%); placebo, 294 of 484 (61%); p = 0.068. In patients in whom treatment was started >12 hours after the onset of pain, opposite trends were found: metoprolol, 140 of 224 (63%); placebo, 111 of 203 (55%); p = 0.123. Data regarding delay time were missing in 8 of the patients in whom MI developed, 3 in the metoprolol group and 5 in the placebo group.

Patients with definite or probable MI (*Fig. 3*): When all patients were analyzed, lower enzyme activity was seen in the metoprolol group (14.8 ± 0.5 μkat·liter^{-1}) than in the placebo group (16.5 ± 0.6 μkat·liter^{-1}; n = 954; p = 0.043). The effect was again restricted to p tients injected within 12 hours (metoprolol, 15.2 ± 0 μkat·liter^{-1}; placebo, 17.4 ± 0.8 μkat·liter^{-1}; p = 0.03 no difference was found among those in whom trea ment was started later.

Electrocardiography (anterior MI): A higher Σ was obtained in patients treated with metoprolol (117 ± 7.6 mm) within 12 hours than in the placebo grou (93.3 ± 6.4 mm; n = 155; p = 0.031), whereas no effe could be demonstrated among those treated later (Fi 4). Similar results were obtained for ΣQ (Fig. 5), a low ΣQ being obtained in the metoprolol group treate within 12 hours (metoprolol, 58.4 ± 7.0 mm; placeb 84.5 ± 7.6 mm; n = 155; p = 0.012), whereas no diffe ence was observed in the remaining patients.

Clinical findings: Tablet treatment was withdraw in 10% in the metoprolol group compared with 6% in t placebo group during the initial hospital stay for t reasons listed in Table III. More patients in the m toprolol group withdrew because of hypotension a bradycardia.

In the metoprolol group (n = 698), 4 patients had be treated with a beta-agonist (prenalterol) because severe reduction of systolic blood pressure in relati to the intravenous dose, compared with 1 patient in t placebo group. In these 4 patients there was a rap restoration of blood pressure after prenalterol trea ment. In 79% of all randomized patients the total do of furosemide given during the first 4 days in the ho pital was calculated. As seen in Figure 6, more fur semide had to be given to placebo patients than to m toprolol patients when treatment was started within hours (metoprolol, 46 ± 6 mg; placebo, 75 ± 8 mg; n 754; p = 0.003), whereas no difference was observed patients treated later.

Table IV compares the 2 groups regarding the dur tion of initial hospitalization in relation to the del from the onset of pain. The metoprolol-treated patien were hospitalized for a significantly shorter period th placebo patients if they received injection ≤4 and ≤ hours after the onset of pain, whereas no difference w observed among patients included later on.

Late infarction: Late nonfatal or fatal MI (onset MI on the fourth day after inclusion in the study later) occurred in 35 patients in the metoprolol grou

Randomly Allocated to Placebo or Metoprolol

Delay (Hours) From Onset of Pain to Blind Injection	Mean Hospital Days (n) ± SEM		Significance (2p)
	Placebo Group	Metoprolol Group	
≤4	11.8 ± 0.5 (172)*	10.3 ± 0.4 (158)	0.036
≤12	11.3 ± 0.4 (451)	10.1 ± 0.3 (442)	0.010
>12	10.5 ± 0.3 (192)	10.9 ± 0.5 (215)	>0.2
All patients	11.0 ± 0.3 (653)	10.3 ± 0.3 (663)	0.073

* Numbers in parentheses refer to number of patients.

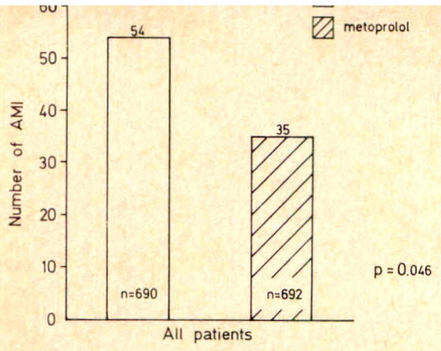

FIGURE 7. Number of patients who developed AMI from day 4 to 90 after inclusion. AMI = acute myocardial infarction.

nd 54 in the placebo group during the 3-month fol-ow-up (p = 0.046) (Fig. 7). Nonfatal late MI occurred n 27 patients in the metoprolol group versus 41 patients n the placebo group (NS). Of the 35 patients in whom late MI developed among those who received me-oprolol, 31 patients had a reinfarction (late MI after an nitial MI), whereas 48 of the 54 patients in the placebo roup were considered to have a reinfarction (NS). Among patients in whom treatment started ≤12 hours fter the onset of pain, late MI developed in 25 me-oprolol-treated patients versus 35 placebo-treated atients. In those in whom treatment was started >12 ours, the number of patients in whom late MI devel-ped was 10 versus 15 in respective groups. Data re-arding the time from onset of pain to the start of reatment were missing in the remaining 4 placebo-reated patients.

Infarct size and 3-month and 1-year survival, espectively (Table V): A similar reduction in 3-nonth mortality was found in patients in whom treat-nent was started within and after 12 hours of the onset f pain. A limitation of indirect signs of the infarct size ould be demonstrated only in patients treated early. When separately analyzing mortality from after 3 nonths to 1 year, during which time all patients re-eived the same treatment, 16 patients originally ran-omized to metoprolol versus 23 patients originally andomized to placebo died in the group treated within 2 hours, whereas 8 metoprolol versus 6 placebo patients ied in the group treated later. There was a significant eduction in the total 1-year mortality rate among pa-tients treated with metoprolol within 12 hours compared with the placebo group, whereas no difference was observed between the 2 groups among patients treated later on.

Correlations: A highly significant correlation among all patients with definite MI was found between peak heat-stable LD and peak CK (r = 0.84; n = 216; p <0.001) (Fig. 8) as well as peak CK B (r = 0.81; n = 204; p <0.001).

A highly significant, although weaker correlation was also found between peak heat-stable LD and ΣR on the fourth day in anterior MI (r = 0.56; n = 179; p <0.001) and ΣQ on the fourth day in anterior MI (r = 0.62; n = 179; p <0.001). There was a high correlation between the peak heat-stable LD value and the area under the 48-hour enzyme curve (r = 0.94; n = 594; p <0.001) and the area under the 108-hour enzyme curve (r = 0.98; n = 450; p <0.001), respectively.

Discussion

In this study 2 independent methods were used to evaluate possible limitation of the infarct size. In awareness of the uncertainty of the 2 methods,[16,17] a comparison between them was made and a significant positive correlation found. Therefore, it was not surprising that the 2 methods gave similar information when the effect of metoprolol on indirect signs of ne-

ABLE V Effect of Early and Late Intervention in Various Subgroups Randomly Allocated to Placebo or Metoprolol

	Delay (Hours) From Onset of Pain to Blind Injection											
	≤4				≤12				>12			
Groups	Placebo	Metoprolol	Effect (%)	2 p	Placebo	Metoprolol	Effect (%)	2 p	Placebo	Metoprolol	Effect (%)	2 p
Heat-stable LD max μkat·liter	14.8 ± 1.0	12.9 ± 0.9	13	0.167	13.3 ± 0.6	11.1 ± 0.5	17	0.009	10.2 ± 0.8	11.2 ± 0.7	−10	>0.2
3-month mortality*	17/181 (9.4)	9/167 (5.4)	43	>0.2	41/484 (8.5)	26/468 (5.6)	34	0.102	20/203 (9.9)	14/224 (6.2)	37	>0.2
1-year mortality	26/181 (14.4)	15/167 (9.0)	38	0.16	64/484 (13.2)	42/468 (9.0)	32	0.047	26/203 (12.8)	22/224 (9.8)	22	>0.2

Missing data regarding time intervals in 2 dead patients (placebo); 1 patient died within 3 months and 1 patient died between 3 and 12 months.
LD = lactate dehydrogenase.

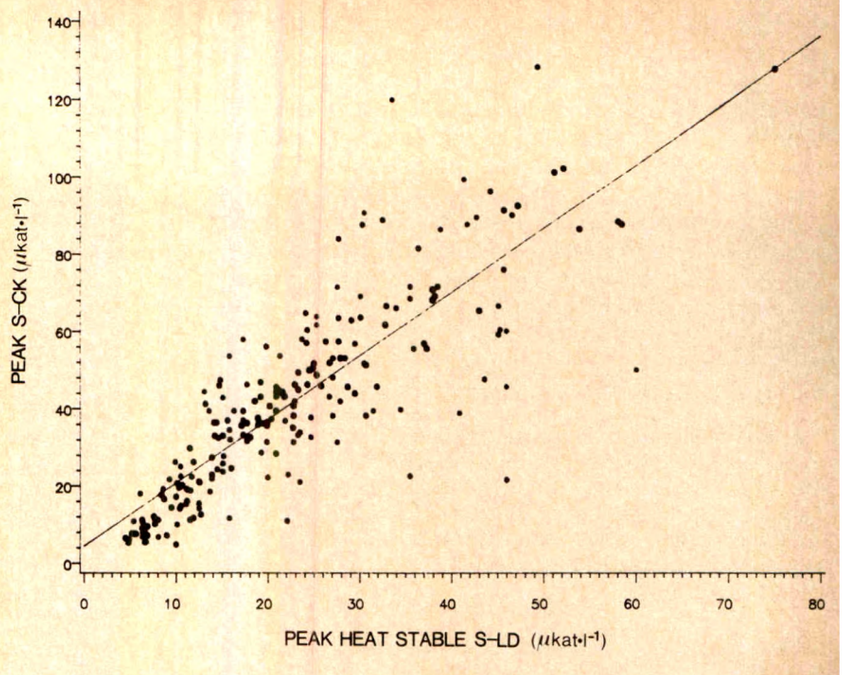

FIGURE 8. Correlation between the peak value of heat-stable serum lactate dehydrogenase (S-LD) and serum creatine kinase (S-CK). n = 216; r = 0.84; p <0.001.

crosis was evaluated. The results are in accordance with those of previous reports.[18,19]

From experience in animal experiments, more pronounced effects could have been expected in patients treated within 4 hours. In a previous report[20] with few patients, results favoring this idea were presented. We found similar results in patients treated within 12 hours compared with those treated within 4 hours. One explanation for this finding might be that patients arriving in the hospital very early have low-flow ischemia in a higher proportion (sudden total coronary obstruction), whereas patients arriving somewhat later have a higher proportion of moderate or high-flow ischemia more apt to receive intervention. Thus, although early intervention is of major importance, other factors might influence the choice of patients suitable for intervention in MI.

It has been argued that beta blockade may increase enzyme clearance and thereby cause lower serum enzyme activity in acute MI.[21] Studies in man do not support this hypothesis.[20] The disappearance rate of heat-stable LD was also similar in the metoprolol group compared with the placebo group in the present study. The possibility that beta blockade may decrease myocardial perfusion and thereby increase local inactivation of enzymes has also been discussed.[20] However, the fact that in this study, as in earlier investigations,[19,20] no effect on enzyme activities was found when the drug was given late speaks against this explanation, as does the observation of metoprolol-induced limitation of Q- and R-wave changes. To determine whether plasma volume was different in treated and nontreated patients, we determined the alpha$_2$-macroglobulin concentration in serum in a small subsample. Treated patients had a similar mean concentration 36 hours after inclusion compared with patients receiving placebo, indicating that metoprolol does not influence the intravasal distribution volume.

It is possible that beta blockade influences the Q and R waves by nonspecific mechanisms not related to the ischemic damage. However, it does seem unlikely that an increase in end-diastolic volume, for example, would result in an increase in the R-wave amplitude and a simultaneous decrease in Q-wave amplitude.

Heart failure was estimated by calculating the dose of furosemide given during the first 4 days. Furosemide is the main diuretic drug used in Sweden for heart failure in patients with MI. The results obtained gave similar information as the enzymes and the electrocardiographic data, namely, a beneficial effect of metoprolol if treatment was started within 12 hours, but not later. Whether or not beta blockade decreases the metabolism of furosemide may be questioned, but if so, why only in patients treated early. Also, beta blockade apparently did not induce cardiac decompensation.

Although no significant reduction was noted in the number of patients in the metoprolol group in whom MI developed during the first 3 days compared with the placebo group, there was a marked reduction in the number of late MI in the metoprolol-treated patients. Although limiting the final size of the infarction with beta blockade seems possible, the intervention probably generally starts too late to prevent the development of MI. Under any circumstances, if the patient is receiving chronic treatment with beta blockade, the drug might protect against new MI, as shown also in the Norwegian timolol trial.[22]

Within 3 months a similar reduction in mortality after treatment with metoprolol was achieved in patients treated early compared with those treated late. A significantly lower 1 year mortality was observed in the metoprolol group included within 12 hours, whereas

on. However, it must be emphasized that the decrease in 1 year mortality might depend to some extent on postinfarct effects of beta blockade during the first 3 months and also that the total number of deaths in the group for which treatment was started after >12 hours was quite small.

Treatment with metoprolol in the acute stage of MI was generally well tolerated. Complications were few and were easily discovered and handled. No difference was seen in the number of patients who had to stop treatment because of heart failure or atrioventricular block, whereas more metoprolol-treated patients withdrew because of hypotension or bradycardia.

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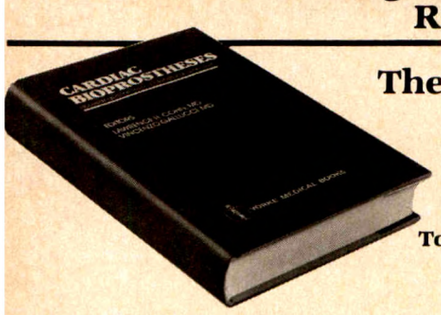

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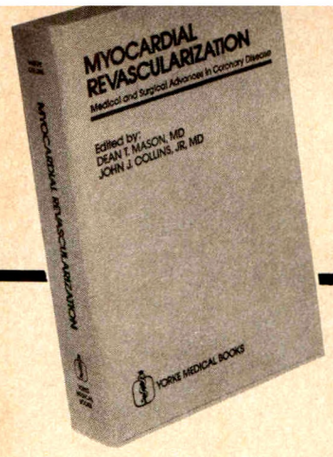

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	methyldopa	WYTENSIN®	In clinical trials to date with WYTENSIN®: Six month, double-blind, multicenter studies.
sodium excretion	↓	—	no sodium retention
plasma volume	↑	—	no plasma volume expansion
weight	↑	↓	no weight gain
glomerular filtration rate	↓	—	no decrease in GFR

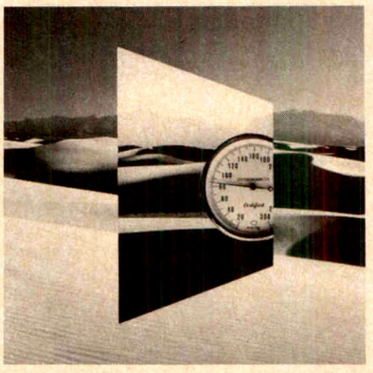
WyTensin®

(guanabenz acetate)

See important information on last page.

Wyeth

management of hypertension



No electrolyte or metabolic risk factors
No long-term cardiovascular risk factors
No immunologic disturbances
No liver damage
No contraindications except hypersensitivity

Side effects are usually mild and transient

Patients may experience drowsiness and dry mouth early during WYTENSIN® (guanabenz acetate) therapy, but these subjective complaints are mostly mild and transient, especially when the initial dosage is *4 mg b.i.d.*, with the second dose at bedtime.

WyTensin®
(guanabenz acetate)

4mg b.i.d.

f Summary

ons:
ensin® (guanabenz acetate) is an orally active
tral alpha-2 adrenergic agonist. Its antihyperten-
action appears to be mediated via stimulation of
tral alpha adrenergic receptors, resulting in a de-
se of sympathetic outflow from the brain at the
ar level to the peripheral circulatory system.
acute antihypertensive effect of **Wytensin** oc-
without major changes in peripheral resistance,
its chronic effect appears to be a decrease in pe-
eral resistance.

ications and Usage:
tment of hypertension, alone or in combination
a thiazide diuretic.

traindication:
wn sensitivity to the drug.

:autions:
dation: Causes sedation or drowsiness in a large
ion of patients. When used with centrally active
essants, e.g., phenothiazines, barbiturates and
todiazepines, consider potential for additive
tive effects.

itients with vascular insufficiency: Like other an-
pertensives use with caution in severe coronary
fficiency, recent myocardial infarction, cerebro-
ular disease, or severe hepatic or renal failure.

ebound: Sudden cessation of therapy with cen-
alpha agonists like **Wytensin** may rarely result
overshoot" hypertension and more commonly
luces increase in serum catecholamines and sub-
ve symptomatology.

ORMATION FOR PATIENTS:
ise patients on **Wytensin** to exercise caution
n operating dangerous machinery or motor ve-
es until it is determined they do not become
sy or dizzy. Warn patients that tolerance for al-
ol and other CNS depressants may be dimin-
d. Advise patients not to discontinue therapy
ptly.

TESTS:
linical trials, no clinically significant lab test ab-
nalities were identified during acute or chronic
apy. Tests included CBC, urinalysis, electrolytes,
T, bilirubin, alkaline phosphatase, uric acid,
, creatinine, glucose, calcium, phosphorus, total
ein, and Coombs' test. During long-term use
e was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction. In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease.

DRUG INTERACTIONS:
Wytensin® was not demonstrated to cause drug interactions when given with other drugs, e.g., digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, potential for increased sedation when given concomitantly with CNS depressants should be noted.

DRUG/LAB TEST INTERACTIONS:
No lab test abnormalities were identified with **Wytensin** use.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9.5 mg/kg/day, i.e., about 10 times maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9.6 mg/kg), suggesting impairment of fertility. Fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy.

PREGNANCY:
Pregnancy Category C:
WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. **Wytensin®** should be used during pregnancy only if potential benefit justifies potential risk to fetus.

NURSING MOTHERS:
Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers.

PEDIATRIC USE:
Safety and effectiveness in children less than 12 years of age have not been demonstrated; use in this age group cannot be recommended.

Adverse Reactions:
Incidence of adverse effects was ascertained from controlled clinical studies in U.S. and is based on data from 859 patients on **Wytensin** for up to 3 years. There is some evidence that side effects are dose-related.

Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n = 102	Wytensin (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less: Cardiovascular—chest pain, edema, arrhythmias, palpitations. Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort. Central nervous system—anxiety, ataxia, depression, sleep disturbances. ENT disorders—nasal congestion. Eye disorders—blurring of vision. Musculoskeletal—aches in extremities, muscle aches. Respiratory—dyspnea. Dermatologic—rash, pruritus. Urogenital—urinary frequency, disturbances of sexual function. Other—gynecomastia, taste disorders.

Drug Abuse and Dependence:
No dependence or abuse has been reported.

Overdosage:
Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both. Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. Adequate airway should be maintained and, if indicated, assisted respiration instituted. No data are available on **Wytensin** dialyzability.

Dosage and Administration:
Individualize dosage. A starting dose of 4 mg b.i.d. is recommended, whether used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response. Maximum dose studied has been 32 mg b.i.d., but doses this high are rarely needed.

How Supplied:
Wytensin® (guanabenz acetate) Tablets, 4 mg and 8 mg, bottles of 100.

CI 3046-1 8/17/82

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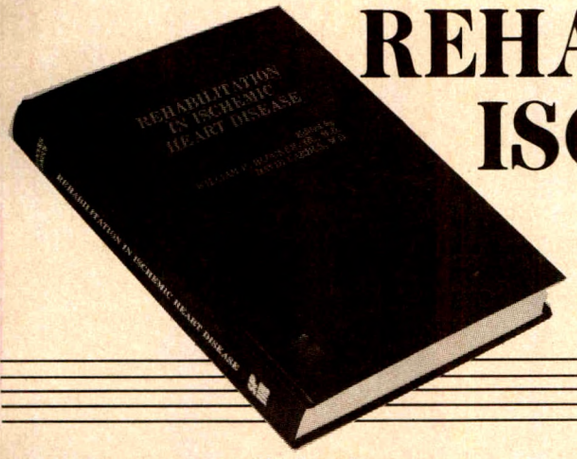
This book contains the most complete list of cardiac risk factors to be found in any text . . .



REHABILITATION IN ISCHEMIC HEART DISEASE

Approx. 500 pp., 188 figs. & tbls., large format 8½x11, 1982, $80.00

Edited by **William P. Blocker, Jr., M.D.,** F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine, Baylor College of Medicine, Houston, and **David Cardus**, M.D., F.A.C.C., Professor of Physiology and Rehabilitation, Baylor College of Medicine, Houston, Texas.

Heavily illustrated, this volume presents 60 self-contained chapters dealing with *all* aspects of rehabilitation of the patient with ischemic heart disease. The 45 noted contributors discuss topics such as: designing a cardiac rehabilitation center; methods of rehabilitation for the stroke patient, amputee, spinal cord injury patient who has had a heart attack; equipment needs for a cardiac rehabilitation center; and legal responsibilities of the physicians and therapists.

All major aspects, from epidemiology and pathogenesis through prevention and education are covered, including ambulatory monitoring of electrocardiogram and blood pressure; evaluation of degree of disability; and pathogenesis of atherosclerosis. This book contains the *most complete* list of cardiac risk factors to be found in any text. This encyclopedic guide to the total care and rehabilitation of cardiac patients is written for *every* member of the cardiac rehabilitation team.

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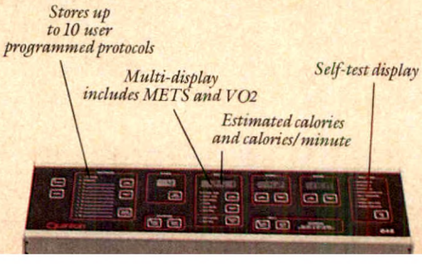

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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS and Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

Before prescribing, please
see full prescribing information.
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"Possibly" effective: For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS:
Acute or recent myocardial infarction, severe anemia, closed-angle glaucoma, postural hypotension, increased intracranial pressure and idiosyncrasy to the drug.

WARNINGS:
Capsules must be swallowed.
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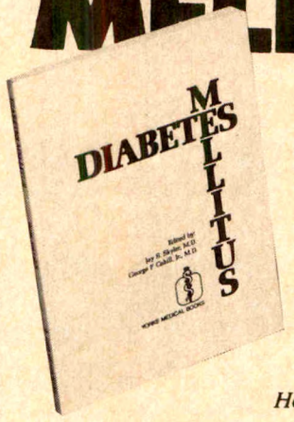

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Role of Myocardial Ischemia in the Genesis of Stress-Induced S-T Segment Elevation in Previous Anterior Myocardial Infarction

HENRY GEWIRTZ, MD, MICHAEL SULLIVAN, MSEE, GEORGE O'REILLY, BSc, STEVEN WINTER, MD, and ALBERT S. MOST, MD

This study tests the hypothesis that myocardial ischemia is responsible for exercise-induced S-T segment elevation in patients with previous anterior myocardial infarction (MI). Exercise stress testing in conjunction with thallium imaging of the myocardium was performed in 28 patients with previously documented anterior MI. Thallium images were analyzed by computer for the presence of initial uptake defects and evidence of abnormal clearance of the isotope from the myocardium (that is, imaging evidence of ischemia). Total S-T segment elevation (ΣST) in precordial leads V_1 to V_6 at rest was subtracted from ΣST at peak stress in order to quantitate the extent of S-T elevation induced by stress (ΔST). Two groups of patients were identified; 1 with stress-induced S-T elevation (Group I, $\Delta ST \geq 4.0$ mm) and 1 without this abnormality (Group II, $\Delta ST < 4.0$ mm). Evidence of abnormal thallium washout from myocardial scan segments occurred in 12 of 15 Group I patients versus 9 of 13 Group II patients (difference not significant). In addition, abnormal tracer washout from anterolateral or septal scan segments occurred in 5 patients in each group. Likewise, abnormal thallium clearance from inferior or posterior scan segments occurred in 8 of 15 Group I patients versus 7 of 13 Group II patients (difference not significant). The patient with the greatest amount of stress-induced S-T elevation (S-T 11.5 mm) had no evidence of ischemia during the stress test. However, Group I patients did have larger anterolateral plus septal initial thallium uptake defect scores than did those of Group II (10 of 15 with defect score ≥ 350 in Group I versus 1 of 13 in Group II, $p < 0.002$). Similarly, resting left ventricular ejection fraction $\geq 30\%$ was present in only 4 of 15 Group I patients versus 13 of 13 in Group II ($p < 0.001$). Finally, multiple stepwise linear regression analysis demonstrated that ΔST correlated best with the extent of initial anterolateral plus septal thallium uptake defect score ($F = 17.3$, $p < 0.001$) and to a lesser extent with resting ejection fraction ($F = 5.2$, $p < 0.05$) and change in heart rate from rest to peak stress ($F = 8.1$, $p < 0.01$; corrected multiple correlation coefficient = 0.76, $p < 0.001$). Thus, in patients with previous anterior MI (1) exercise-induced myocardial ischemia occurs as often with as without S-T segment elevation, (2) myocardial ischemia is not required for the production of stress-induced S-T segment elevation, and (3) stress-induced S-T elevation primarily reflects the extent of previous anterior wall damage and to a lesser extent an increase in heart rate between rest and peak stress.

Persistent S-T segment elevation in anterior precordial leads is not uncommon after anterior myocardial infarction (MI)[1] and is a specific albeit insensitive indicator of underlying left ventricular aneurysm.[2–5] Although myocardial ischemia does not appear to play a role in the genesis of chronic S-T segment elevation in these patients,[6] the role of ischemia in exercise-induced additional or new S-T segment elevation is less clear. While previous investigators have stated that myocardial ischemia does not contribute to this phenomenon,[7,8] a recent preliminary report[9] as well as several older reports[10–12] indicate that ischemia may be involved. Accordingly, the present study was undertaken to test the hypothesis that myocardial ischemia is responsible for exercise-induced S-T segment elevation in anterior precordial leads in patients with previous anterior MI.

From the Rhode Island Hospital, Department of Medicine (Cardiology Section), and Brown University Program in Medicine, Providence, Rhode Island. Manuscript received August 27, 1982; revised manuscript received January 14, 1983, accepted January 17, 1983.

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Methods

Patient population: The study population consists of 28 atients (27 men, 1 woman) with a mean age of 53 years (range 7 to 79). Patients were selected on the basis of a history of revious anterior MI documented by standard electrocardiographic and enzyme criteria. These patients represent a ubset of all patients referred to the cardiovascular Nuclear Medicine laboratory at Rhode Island hospital by their private hysician for clinically indicated thallium stress tests and esting multigated cardiac blood pool scans. Radionuclide tudies were performed within 1 month of each another in 15 atients and within 2 to 9 months (mean 5) in the remainder. The time between MI and thallium stress test ranged from 1.5 o 120 months (mean 13).

Exercise stress test protocol: Each patient underwent a ymptom-limited, maximal exercise stress test according to modified Bruce protocol. Before the stress test a 12-lead lectrocardiogram (ECG) was obtained along with an interval istory and physical examination with attention directed oward the cardiovascular system. Thallium stress tests were erformed on a bicycle ergometer (Warren E. Collins, Braintree, Massachusetts) with the patient in the upright osition. Exercise was begun at 150 kpm and was increased y 150 kpm every 3 minutes. Heart rate, blood pressure (cuff), nd 12-lead ECG were recorded at 2.5 minutes into each stage f exercise. The patients' medications were continued as rescribed. Seventeen patients were taking digitalis or diuretics or both at the time of the thallium stress test. Informed onsent to undergo an exercise stress test in conjunction with adionuclide imaging of the heart was obtained from each atient.

Analysis of electrocardiograms: Because patients with lectrocardiographic evidence of anterior MI frequently have recordial lead S-T segments that demonstrate continuous psloping from the J point and that merge imperceptibly with ne T wave, we measured S-T segment elevation at the J point ather than 80 ms after it. The P-R segment was used as the oelectric point for this measurement. S-T segment elevation precordial leads V_1 through V_6 was summed (ΣST) and the esulting value subtracted from the sum of S-T segment elevation in the same leads in the immediate poststress electrocardiogram. The absolute value of the difference (ΔST) indicates the magnitude of additional S-T segment elevation hich occurred with stress in each patient. The immediate oststress ECG was used to evaluate the response of the S-T gment to exercise, because records obtained at peak stress equently exhibited baseline drift and muscle artifact which ake it difficult to accurately measure S-T segment elevation. atients in whom the absolute value of ΔST was ≥ 4 mm were efined as having additional S-T segment elevation in response to stress. Those in whom <4 mm of additional S-T evation occurred were defined as having no additional S-T evation with stress. The method of electrocardiographic alysis was chosen to obtain as much information as possible om the 6 precordial electrocardiographic leads while eliminating the possibility that any patient would be classified as aving stress-induced S-T elevation on the basis of only slight hat is, ≤ 0.5 mm) changes in repolarization potentials in veral or even all precordial leads. Although this definition S-T elevation admittedly is arbitrary, it does have the adntage of (1) using data from all 6 precordial leads and (2) ing more conservative than criteria of previous investigators[7,8] who accepted ≥ 1 mm S-T segment elevation in only a ngle electrocardiographic lead as evidence of new or increased S-T segment elevation with stress.

Thallium imaging: data acquisition and analysis: One inute before discontinuation of exercise, 2 mCi of thallium-201 was injected intravenously. After injection of the isotope the patient continued to exercise for an additional minute and then stopped. Imaging, first in the anterior and then in the 50° left anterior oblique position, was begun 5 to 7 minutes after thallium injection. Delayed images were obtained 2 to 3 hours later. All images were acquired in a 128 by 128 computer matrix (Medical Data Systems, Ann Arbor, Michigan) for 300,000 counts and acquisition time was carefully noted. An Ohio Nuclear Series 420 gamma camera equipped with a parallel hole, general all purpose collimator was used for this purpose.

The computer also was used to analyze the thallium images for the presence and location of initial uptake defects and for changes in thallium activity over time. Image analysis was performed without knowledge of the results of the electrocardiographic response to stress. The method for analyzing the thallium scan was similar to that described by previous investigators.[13,14] In brief, the images were first "zoomed" into a 64 by 64 matrix and then smoothed using a commercially available 9-point smoothing algorithm. Scans were then background corrected using a modified bilinear interpolative technique.[15] Next a radial analysis routine was employed to assess both uptake and washout of thallium at each 6° arc along the myocardial images. Uptake or washout abnormalities or both were said to be present when 2 or more adjacent radii fell below 2 standard deviations of the mean value of thallium uptake or washout at a given radial location for normal patients (n = 14) studied in our laboratory. The intra- and interobserver agreement for this method of image analysis ranges between 77 and 80% in our laboratory.[16] Delayed washout of thallium from myocardial scan segments was taken as objective evidence of tracer redistribution,[17,18] and thus was used as an independent test for determining if (and where) myocardial ischemia occurred during the stress test. Scan segments exhibiting delayed washout of thallium have been shown to correspond well with regions of myocardium perfused by stenosed ($\geq 50\%$ luminal diameter reduction) coronary arteries.[13,16]

Radionuclide ventriculography: data acquisition and analysis: Resting multigated cardiac blood pool scans were obtained after in vivo labeling of the patients' red blood cells with 25 m Ci of technetium-99m pertechnetate. Commercially available software (MUGB program) was used for this purpose. Images were obtained in anterior and 45° left anterior oblique projections with an Ohio Nuclear Series 420 gamma camera equipped with a parallel hole, general all purpose collimator and interfaced with the MDS computer system. Images were acquired for 200,000 counts/frame in a 32 by 32 matrix. Left ventricular ejection fraction was determined from the left anterior oblique view, using commercially available software (MUGE program).

Statistical analysis: A stepwise linear multiple regression analysis was used to assess the significance of correlations between the extent of S-T segment elevation induced by stress and various other experimental parameters. The Fisher exact test was used to assess the statistical significance of 2 by 2 frequency distributions. All data are expressed as mean $\pm$ 1 standard deviation. P values <0.05 were considered statistically significant.

Results

Clinical and electrocardiographic data: In response to stress 15 of 28 patients developed ≥ 4 mm S-T segment elevation over and above that present on the resting tracing (Group I). The remaining 13 patients developed <4 mm S-T segment elevation in precordial leads V_1 through V_6 in response to stress (Group II).

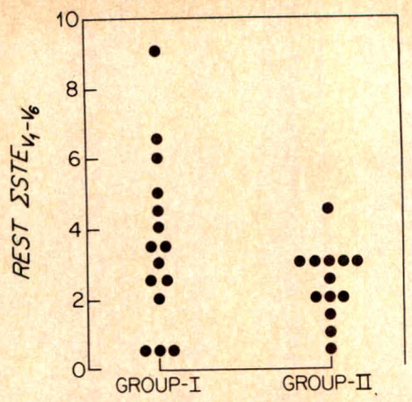

FIGURE 1. Total S-T segment elevation (ΣST) (mm) at rest in precordial leads V_1 through V_6 is plotted for each individual in the study. Note that ≤3.0 mm total S-T segment elevation at rest was more frequent in Group II patients (12 of 13 [92%]) than in those in Group I. Nevertheless, 7 of 15 (46%) Group I patients also had only limited (≤3.0 mm) S-T segment elevation at rest.

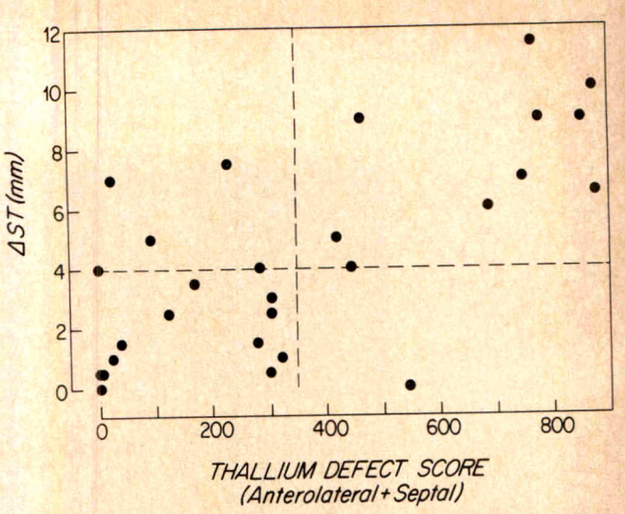

FIGURE 2. Combined anterolateral plus septal thallium scan initial uptake defect score (arbitrary units) is plotted on the abscissa versus ΔST on the ordinate for each patient. The correlation coefficient was 0.63 ($p < 0.001$). A defect score >350 was present in only 1 of 13 (8%) Group II patients versus 10 of 15 (67%) in Group I ($p < 0.005$).

Concomitant S-T segment depression ≥1 mm at 80 ms after the J point occurred in inferior limb leads (II, III, and aVF) or lateral precordial leads (V_5 and V_6), or both, in 7 patients (3 in Group I versus 4 in Group II; p not significant [NS]). The change in heart rate between rest and peak stress did not differ significantly between the 2 groups (60 ± 21 min^{-1} in Group I versus 47 ± 27 min^{-1} in Group II). Furthermore, 8 of 15 patients in Group I attained 85% of maximal age-predicted heart rate in comparison with 3 of 13 Group II patients (p = NS). Twelve patients experienced angina pectoris during the stress test (7 in Group I versus 5 in Group II). Similarly, 9 of 15 patients in Group I were taking digitalis at the time of their stress test in comparison with 6 of 13 in Group II. Diuretics were taken by 7 patients in Group I versus 5 in Group II. Total S-T segment elevation in precordial leads V_1 through V_6 at rest was >3 mm in 8 of 15 patients in Group I in comparison with only 1 of 13 patients in Group II ($p < 0.01$). However, there was overlap between the 2 groups in this regard (Fig. 1) and there was no correlation between ΣST at rest and ΔST in response to stress.

Imaging data: An initial anterolateral and/or septal thallium uptake defect was present in 14 of 15 Group I patients and in 10 of 13 Group II patients. Evidence of thallium redistribution (that is, delayed or slow washout of isotope over the course of time) occurred in 12 of 15 Group I patients and in 9 of 13 Group II patients. Also, evidence of thallium redistribution into anterolateral or septal scan zones occurred in 5 patients in each group. Likewise, redistribution into inferior or posterior scan zones occurred in 8 of 15 Group I patients and in 7 of 13 Group II patients. However, patients in Group I had higher combined anterolateral plus septal thallium initial uptake defect scores (Fig. 2) than did patients in Group II (combined score >350 arbitrary units in 10 of 15 Group I patients versus 1 of 13 Group II patients, $p < 0.002$). Furthermore, only 4 of 15 Group I patients had resting ejection fractions ≥30% (Fig. 3) in comparison with 13 of 13 Group II patients ($p < 0.001$). Stepwise linear multiple regression analysis demonstrated that ΔST correlated best with size of initial anterolateral plus septal scan defect ($F = 17.3$, $p < 0.001$) and to a lesser extent with resting ejection fraction ($F = 5.2$, $p < 0.05$) and change in heart rate from rest to peak stress ($F = 8.1$, $p < 0.01$). The corrected multiple correlation coefficient (r) for the regression of ΔST on size of initial anterolateral plus septal scan defect score, resting ejection fraction, and change in heart rate was 0.76, $F = 13.5$, $p < 0.001$.

Discussion

In an earlier study the extent of S-T segment elevation in patients with persistent S-T segment elevation after anterior MI was not altered by interventions that modified myocardial oxygen supply-demand balance.[6]

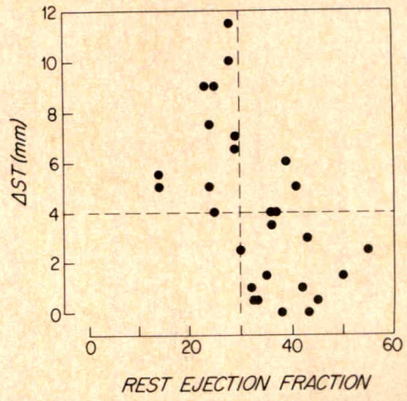

FIGURE 3. Resting left ventricular ejection fraction is plotted on the abscissa versus ΔST on the ordinate for each individual in the study. The correlation coefficient was − 0.52 ($p < 0.01$). All patients in Group II had ejection fractions ≥30%, versus only 4 of 15 (27%) in Group I ($p < 0.001$).

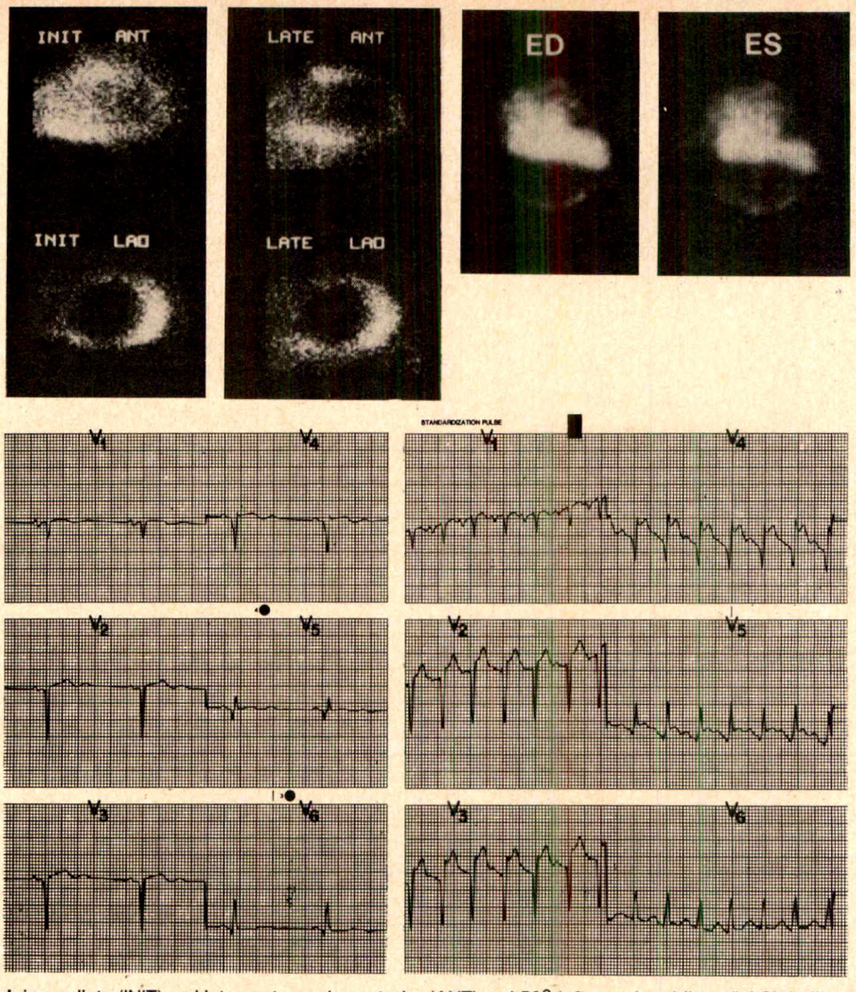

FIGURE 4. Top left panel, immediate (INIT) and late postexercise anterior (ANT) and 50° left anterior oblique (LAO) thallium images from the patient with the highest value of ΔST observed in the study. Note the extensive initial uptake defect involving anterolateral, apical, septal, and apical-inferior scan segments in the anterior and LAO projections. The initial scans also demonstrate dilation of the left ventricle and increased tracer uptake by the lungs in the anterior view. The latter finding suggests the occurrence of left ventricular failure during the stress test.[21] **Top right panel,** end-diastolic (ED) and end-systolic (ES) images (anterior view) from the patient's resting multigated cardiac blood scan. The left ventricle is enlarged and exhibits an obvious aneurysm at its apex with extension along the anterolateral and inferior wall. **Bottom panel,** rest (**left**) and peak stress (**right**) precordial leads V_1 through V_6 of the electrocardiogram are shown here for the patient with the highest value of ΔST observed in the study. Marked S-T elevation was induced by stress in leads V_2 through V_5 even though only modest S-T segment elevation was present on the resting trace.

Accordingly, it was concluded that chronic myocardial ischemia was unlikely to be responsible for this electrocardiographic abnormality. However, the observation that resting S-T segment elevation in these patients is not related to myocardial ischemia does not exclude the possibility that additional (or new) S-T elevation is caused by stress-induced myocardial ischemia. In addition, the observation that stress-induced S-T segment elevation in patients with previous anterior MI may be abolished after successful coronary bypass surgery also suggests a possible role for myocardial ischemia in this phenomenon.[9] However, the results of the present study indicate that myocardial ischemia is not sufficient by itself to cause additional S-T segment elevation in patients with previous anterior MI. Indeed, although 21 of 28 patients studied had evidence of abnormal myocardial washout of thallium (that is, imaging evidence of myocardial ischemia[17,18]), only 11 of 21 (52%) exhibited evidence of increased or new S-T segment elevation during the stress test. Furthermore, the patient who exhibited the greatest degree of S-T segment elevation in response to stress (ΔST = 11.5 mm) had no evidence of thallium redistribution in either anterior or left anterior oblique images (Fig. 4). Thus, although we cannot exclude the possibility that ischemia may contribute to additional or new S-T segment elevation during stress testing in some patients with previous anterior MI, clearly this phenomenon (that is, stress-induced S-T segment elevation) may occur in the absence of any evidence of myocardial ischemia.

Although this study was not designed specifically to determine the precise mechanism responsible for stress-induced new or increased S-T segment elevation in patients with previous anterior MI, data suggest that the following factors may be operative. First, there was a trend for patients with more extensive uptake defects

on thallium scans to exhibit increased S-T segment elevation in response to stress (Fig. 2). Thus, patients who exhibited ≥4 mm additional S-T elevation (Group I) also were more likely to have larger thallium initial defect scores for the anterolateral plus septal scan zones in comparison with patients with <4 mm additional S-T segment elevation (Group II). Similarly, Group I patients tended to have lower left ventricular resting ejection fractions than did those in Group II (Fig. 3), an observation that also is consistent with more extensive myocardial damage in the former group in comparison with that in the latter group.

The mechanism by which more extensive left ventricular damage contributes to increased S-T segment elevation during stress is unclear. However, it is known that body surface potentials are increased by increases in left ventricular volume (Brody effect[19,20]). Because patients with increased S-T segment elevation with stress tend to have more extensive left ventricular damage (Fig. 4), they also may be more likely to develop left ventricular dilation in response to stress than are patients in whom myocardial damage is less extensive. Thus, differences in stress-induced changes in left ventricular volume could potentially account for differences observed between the 2 groups in the extent of S-T segment elevation which occurs during exercise. However, additional studies are required to test this hypothesis.

The clinical implications of the data may be summarized as follows. Myocardial ischemia as evidenced by abnormal clearance of thallium from myocardial scan segments is common in patients with previous anterior MI. Increased S-T segment elevation in response to stress testing also is relatively common and (as defined in this study) occurred in 50% of the patients. However, the relation between the 2 events (that is, myocardial ischemia and increased S-T segment elevation) appears more coincidental than causal. Specifically, although 12 of 15 patients with increased S-T segment elevation had evidence of ischemia on thallium study, 10 of 21 patients with ischemia on thallium study failed to exhibit increased S-T segment elevation during stress. Furthermore, as just pointed out, the individual with the greatest increase in S-T segment elevation had no evidence of ischemia on the thallium scan nor did he complain of chest discomfort during the test. Accordingly, although ischemia could contribute to increased S-T segment elevation during stress in some patients, it clearly is not required. Furthermore, ischemia frequently occurs in the absence of increased S-T segment elevation in this group of patients. However, increased S-T segment elevation in response to stress does indicate the presence of extensive left ventricular damage and generally more severe impairment of resting left ventricular systolic function. Finally, differences in the extent of left ventricular dilatation induced by stress may be responsible for differences in S-T segment response to stress in patients with previous anterior MI.

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Enzymatic Estimation of Myocardial Infarct Size Whe Early Creatine Kinase Values Are Not Available

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Estimates of myocardial infarct (MI) size based on plasma creatine kinase (CK) are used widely for prognosis and in the assessment of therapy designed to salvage ischemic myocardium. However, if the initial plasma CK activity is elevated, MI size will be underestimated. To determine the impact of loss of early CK values on estimates of MI size and to develop a procedure to compensate for it, estimates of MI size based on complete and incomplete MB and total CK time-activity curves from 120 patients (experimental group) were compared. Estimates of MI size based on data inclusion intervals beginning at 24, 12, 8, and 4 hours before peak CK were 11, 14, 23, and 47% smaller than values based on complete CK curves, but the correlation was good between complete and incomplete estimates of MI size at any given interval, with r values ranging from 0.91 to 0.98. The derived correction fact then prospectively applied to a new popu = 25) with complete CK curves to compe purposely omitted early CK values. The c estimates of MI size were within 7% of tho on the complete CK curves. Similar resu obtained for transmural and nontransm anterior or inferior MI. Thus, if peak plasr known, underestimation of MI size can pensated for despite the unavailability of values. Since >90% of patients presen plasma CK has reached its peak (24 hours can be obtained in nearly all patients. Thu able to correct for unavailable early CK makes MI size a more widely applicable for use in clinical trials and patient manag

Myocardial infarct (MI) size estimated from serial changes in plasma creatine kinase (CK) is a frequently used endpoint for assessment of interventions designed to influence ischemic myocardium.[1–11] Enzymatic estimates of MI size correlate with short- and long-term prognosis,[12–16] the severity of ventricular dysfunction,[17,18] the incidence of ventricular arrhythmias,[19] and the incidence of heart failure.[20,21] Their reliability has been confirmed in postmortem studies demonstrating concordance between enzymatic and morphometric estimates.[15–22] Availability of enzymatic est MI size permit assessment of therapeutic inte with smaller numbers of patients than requ alternative conventional endpoints such as m The widespread availability of convenient, r quantitative CK isoenzyme assays has made e estimation of MI size widely applicable.[24,25]

In 1978 a randomized, multicenter study limitation of infarct size (MILIS) was implem the National Heart, Lung, and Blood Institute the effects of propranolol and hyaluronidase o in patients with acute MI. The primary endpo study is MI size determined by analysis of seri CK changes. Several other variables are also including ventricular function and rhythm. MILIS will not be completed until 1983, inte ysis of data, without stratification of patie treatment or control groups and without unl indicated that in approximately 20% of the pat initial plasma CK value was elevated. The

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available earlier values leads to underestimation of MI size. Elevation of CK activity in the initial CK sample possibly occurs even more frequently in the general hospital patient population.

This study characterizes the quantitative impact of loss of early CK data on estimates of MI size and develops and evaluates a practical correction process to compensate for early data loss. Complete plasma CK curves from a large sample of patients were analyzed to provide estimates of MI size based on complete sets of data. The effect on estimates of omitting early CK values was then determined. The correction method was validated prospectively in a separate group of patients with acute MI.

Methods

The clinical centers participating in MILIS are the Brigham and Women's Hospital, the Massachusetts General Hospital (Boston, Massachusetts), the University of Vermont (Burlington, Vermont), Barnes Hospital (St. Louis, Missouri), and Parkland Memorial Hospital (Dallas, Texas). All patients entering the cardiac care units of these hospitals are considered potential participants. Patients eligible for enrollment must (1) have typical chest pain lasting for ≥30 minutes; (2) have electrocardiographic changes consisting of new ST-T segment changes ≥1 mm, new Q waves, or new left bundle branch block; and (3) be admitted within 18 hours of onset of symptoms. Patients are excluded for any of the following reasons: (1) age >75 years; (2) Killip class IV congestive heart failure; (3) pregnancy; (4) advanced or terminal illness; (5) cardiomyopathy, acute cerebrovascular disease, or concomitant use of an artificial pacemaker; (6) myocardial infarction within 2 weeks; (7) physical or psychological inability to cooperate with the study, or (8) concurrent participation in another research protocol.

Data are collected in a standardized fashion at all clinical centers. Laboratory data are obtained and processed at separate reference laboratories, and blinded with respect to patient stratification and treatment. All data are collated and analyzed at an independent data coordinating center with tabulation identified only by patient number.

Patient population: Patient selection for the present study was based solely on the characteristics of the plasma total and MB CK time-activity curves. All had complete curves, defined as those with an initial total CK value of ≤100 IU/liter and an initial MB CK value of ≤12 IU/liter, inclusion of all values including peak, and subsequent return to a value at or below the initial baseline value.

Initial assessment and data analysis were performed on curves from 120 patients enrolled in MILIS whose plasma CK curves met these criteria (the experimental group). A second group of patients, referred to as the test group, consisted of an independently acquired sample of 25 patients with definite myocardial infarction and complete total and MB CK time-activity curves, admitted to the Barnes Hospital Cardiac Care Unit between August 1, 1978 and March 1, 1979. The test group included patients who were excluded from enrollment into MILIS primarily because of patient or physician refusal. The criteria for confirmation of myocardial infarction in this test group were the same as those used for MILIS, namely, typical serial elevations of plasma total and MB CK. MI was deemed transmural if new Q waves developed and nontransmural if electrocardiographic changes were restricted to the ST-T segment. MI was designated as anterior when diagnostic changes involved leads V_1 to V_5, and inferior when they involved 2 or more of leads 2, 3, or aVF.

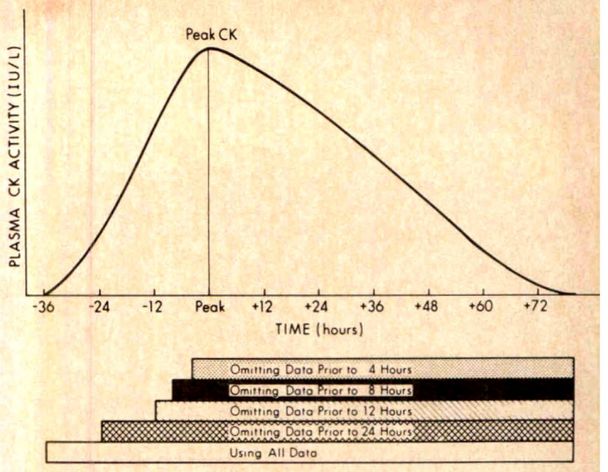


FIGURE 1. The approach used to determine the effect of omitting earl CK data on estimates of MI size. As indicated, peak plasma CK activit was used as the reference point, and estimates of MI size based o inclusion of data beginning 4, 8, 12, or 24 hours before peak wer compared with estimates on all values.

Collection and analysis of CK and MB CK samples Blood samples for total and MB CK analysis were draw hourly for the first 4 hours after admission, every 2 hours fo the next 4 hours, and every 4 hours subsequently, for an in terval of 96 hours from the time of initial sample. Sample were then obtained every 12 hours until hospital discharge Blood samples were drawn into a tube containing ethyleneg lycoltetraacetic acid (5 m*M*) and centrifuged for 10 minute at 2,500 *g* to remove the cellular components. Before storage beta-mercaptoethanol (final concentration = 10 m*M*) wa added and samples were stored at −20°C. Samples wer shipped on dry ice to the MILIS CK Core Laboratory a Washington University. Selected samples are returned peri odically to the clinical units and after storage reshipped to th CK Core Laboratory for repeat analysis. To date, results o CK analysis before and after shipping and storage remai within 5%. Plasma total CK activity was determined spec trophotometrically by the method of Rosalki.[26] MB CK wa analyzed quantitatively by 2 methods: a glass bead batc absorption assay[27] and a radioimmunoassay.[28] For estimatio of MI size, all CK values before return to baseline usuall within 96 to 144 hours were included. The MB CK value utilized for estimating MI size were those determined by th glass bead method.

Analytical approach: Total and MB plasma CK curve were analyzed separately, but the approach employed wa identical. Peak plasma CK activity was identified and the tim to peak determined for each curve, defined as the interva from initial elevation of plasma total or MB CK above baselin to the time of occurrence of peak CK activity. To determin the impact of loss of early enzyme data on values for MI size several estimates of MI size were computed for each patien in the experimental group. Estimates based on all data point are termed, for convenience, complete estimates. Subse quently, separate estimates of MI size (incomplete estimates were obtained based on inclusion of only the initial 24, 12, 8 or 4 hours of data before peak (Fig. 1). Thus, 5 estimates of M size were obtained for each patient, 1 based on the complet CK curve and the others based on incomplete data sets. In complete estimates at each interval of data exclusion wer compared with complete estimates. The extent of underesti mation of MI size obtained from each set of incomplete esti

TABLE I Comparison of Complete and Incomplete Estimates of MI Size Based on Total CK in the Experimental Group

Onset of Interval of Data Inclusion	Infarct Size (CK-g-Eq)	Percent Under-estimation	Correlation Between Estimates With Complete and Incomplete CK Curves (r)
Before initial CK elevation (all values)	44 ± 3	0	. . .
24 hours before peak CK	40 ± 3	11 ± 1	0.98
12 hours before peak CK	38 ± 4	14 ± 2	0.95
8 hours before peak CK	34 ± 4	23 ± 2	0.98
4 hours before peak CK	26 ± 3	47 ± 2	0.96

TABLE II Comparison of Complete and Incomplete Estimates of MI Size Based on MB CK in the Experimental Group

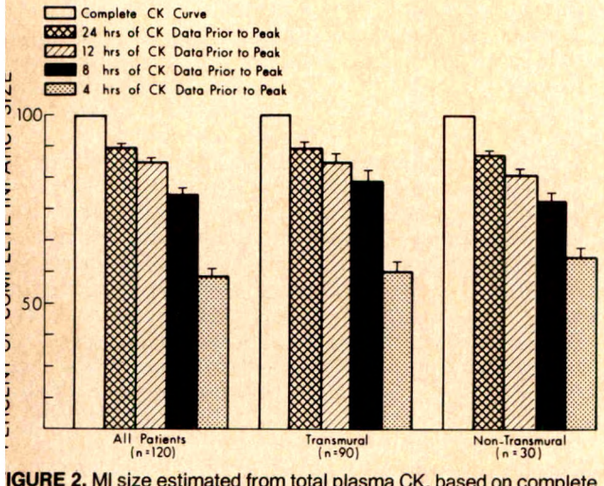
Onset of Interval of Data Inclusion	Infarct Size (CK-g-Eq)	Percent Under-estimation	Correlation Between Estimates With Complete and Incomplete MB CK Curves (r)
Before initial MB CK elevation (all values)	43 ± 3	0	. . .
24 hours before peak MB CK	39 ± 3	10 ± 1	0.96
12 hours before peak MB CK	37 ± 3	14 ± 1	0.94
8 hours before peak MB CK	33 ± 4	24 ± 2	0.95
4 hours before peak MB CK	22 ± 3	49 ± 2	0.92

nates was expressed as the percentages of the corresponding omplete estimates. The inverse of percentages were consid-red to be potential "correction factors." An identical analysis vas performed on complete curves from 25 other patients tudied prospectively and referred to as the test group.

To assess utility of the correction factors, early data were mitted from the plasma CK curves in the test group. Esti-nates of MI size based on the incomplete curves were adjusted y utilizing the correction factors derived from the experi-nental group. The adjusted estimates were then compared vith estimates from the complete curves in the test popula-ion.

MI size based on total or MB CK was estimated as previ-usly described in detail.[28] Complete and incomplete esti-nates of MI size were analyzed for all patients and for those atients with anterior, inferior, transmural, and non-ransmural MI to determine whether site and locus of MI in-luenced the values of the derived correction factors.

Statistics: Values are expressed as a mean ± standard de-iation unless indicated otherwise. The *t* test for unpaired amples was used to compare intergroup data. Linear re-gression analysis was performed to determine the correlation coefficients for relations between complete and incomplete estimates of MI size.



IGURE 2. MI size estimated from total plasma CK, based on complete nd incomplete CK data, is compared for the total population in the xperimental group (all patients) and for patients with transmural and ontransmural infarction. The results show that a similar underesti-nation of MI size (shown on the **ordinate**) occurs with transmural and ontransmural MI for each specific interval of data included.

Results

Experimental group—effects of omission of early data: The mean values for complete and incomplete estimates of MI size in the experimental group are shown in Table I. As indicated by the high values of the correlation coefficients, estimates for each interval of data exclusion correlate closely with complete estimates. Mean MI size, based on complete total CK curves, was 44 ± 3 CK-g-Eq, with a range of 4 to 146, representative of the range for the overall MILIS population and similar to previously published results.[13,16] Initial plasma CK elevation occurred 5.8 ± 0.4 hours after the onset of symptoms, with a range of 1 to 11. Peak plasma CK occurred 23 ± 1 hours after the initial CK elevation, that is, an average of 29 hours after the onset of symptoms (range 13 to 33). The percent difference between complete and incomplete estimates of MI size is illustrated in Figure 2. Estimates of MI size based on CK data beginning only 24 hours before peak CK averaged 40 ± 3 CK-g-Eq, that is, 11 ± 1% less than the corresponding value based on complete data. Estimates based on CK data beginning only 12 hours before peak averaged 38 ± 4 CK-g-Eq, that is, 14 ± 2% less than the complete data estimate. Estimates based on CK data beginning only 8 hours before peak averaged 34 ± 4 CK-g-Eq, that is, 23 ± 2% less than the corresponding complete data estimate. An even more marked underestimation of 47 ± 2% resulted when data beginning only 4 hours before peak were employed.

Striking differences were evident between estimates of MI size based on MB CK from incomplete compared with complete data sets, as shown in Table II. Nevertheless, the correlation between the values for any given interval and complete estimates was close. Complete estimates based on MB CK averaged 43 ± 3 CK-g-Eq, with a range of 1 to 80. Initial plasma MB CK elevation occurred 5.8 ± 0.4 hours after the onset of symptoms, with a range of 1 to 11, similar to that for total CK. Peak plasma MB CK occurred 29 ± 1 hours after the onset of symptoms. The mean difference between complete

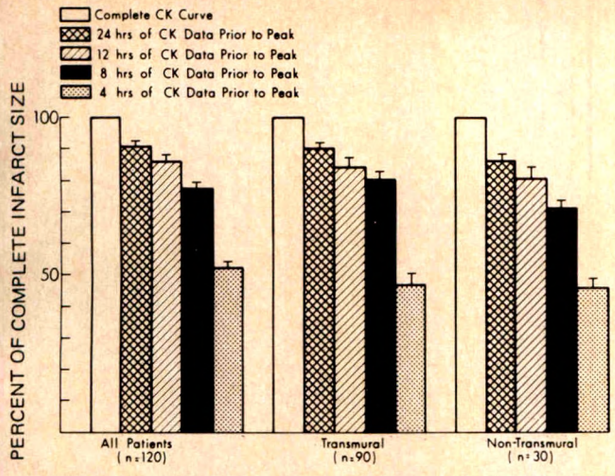


FIGURE 3. Infarct size estimated from MB CK, based on complete and incomplete CK data, is compared for the total population in the experimental group (all patients) and for patients with transmural and nontransmural MI. A similar underestimation of MI size (shown on the **ordinate**) occurs with transmural and nontransmural infarction for each specific interval of data included.

TABLE III Comparison of Complete and Incomplete Estimates of MI Size in the Test Group

Onset of Interval of Data Inclusion	Infarct Size (CK-g-Eq)	Percent Underestimation	Correlation Between Estimates With Complete and Incomplete CK MB Curves (r)
Before initial CK elevation (all values)	40 ± 6	0	. . .
24 hours before peak CK	37 ± 5	8 ± 2	0.93
12 hours before peak CK	35 ± 5	15 ± 1	0.91
8 hours before peak CK	27 ± 3	25 ± 3	0.93
4 hours before peak CK	19 ± 3	51 ± 3	0.95
Before initial MB CK elevation (all MB CK values)	41 ± 7	0	. . .
24 hours before peak MB CK	38 ± 5	8 ± 1	0.91
12 hours before peak MB CK	35 ± 4	14 ± 1	0.92
8 hours before peak MB CK	26 ± 3	23 ± 1	0.95
4 hours before peak MB CK	18 ± 3	48 ± 1	0.93

and incomplete estimates of MI size with data from only the intervals embracing 24, 12, 8, and 4 hours before peak MB CK were 10.5 ± 0.4, 14 ± 1, 24 ± 2, and 49 ± 2%, as shown in Figure 3.

In the experimental group, MI was transmural in 90 patients and nontransmural in 30. Mean MI size based on total plasma CK in patients with transmural MI averaged 47 ± 4 CK-g-Eq, significantly greater than that in patients with nontransmural MI (22 ± 4 CK-g-Eq, $p < 0.004$). A similar difference was observed for estimates based on MB CK (45 ± 2 CK-g-Eq for transmural and 23 ± 2 CK-g-Eq for nontransmural MI, $p < 0.002$). No significant difference in this variable was observed among patients with anterior, inferior transmural, or anterior or inferior nontransmural MI (Table III).

The differences in the time to peak CK or to peak MB CK in patients with transmural compared with nontransmural MI did not significantly change the derived correction factors. Underestimation of MI size with data from only 24, 12, 8, or 4 hours before peak averaged 10, 15, 21, and 50% in patients with transmural compared with 13, 19, 27, and 45% among those with nontransmural MI. Corresponding percentages of underestimations where MB CK values were used were 10, 16, 20, and 53% for transmural and 14, 19, 29, and 54 for nontransmural MI. Although the percentage of underestimation for both MB CK and total CK for nontransmural was somewhat greater than that in transmural MI and in the group as a whole, the mean values were not statistically different.

Test group: Analysis of the test group is shown in Table IV for total and MB CK. Complete estimates of MI size in the test group averaged 40 ± 6 CK-g-Eq, with a range of 4 to 121, which was similar to values in the experimental group. The time to peak plasma total CK activity was 24 ± 1 hours. Incomplete estimates for the inclusion intervals of only 24, 12, 8, and 4 hours of data before peak total CK averaged 8 ± 2, 15 ± 1, 25 ± 3, and 51 ± 3%, that is, less than values for complete estimates. Again, the correlation was close between complete and incomplete estimates of MI size for any interval selected. The percentages of underestimation of MI size in the test group were virtually identical to those in the experimental group (Fig. 4).

Results of analysis of plasma MB CK curves for the test group are shown in Table IV. Mean values for complete estimates of MI size were 41 ± 7 CK-g-Eq, with a range of 2 to 80. The time to peak MB CK was 24 hours. The extent of underestimation of MI size at the selected intervals of omitted MB CK data was identical to underestimation in the total CK. The correlation between incomplete and complete estimates for any given interval was close.

The interval to peak CK in patients with transmural MI in the test group averaged 25 ± 1 hours, as opposed to 17 ± 2 for patients with nontransmural MI. These values are similar to those in the experimental group.

Correction of incomplete estimates: Figure 5 shows the relation between underestimation of MI size

TABLE IV Influence of Site and Type of MI on Time to Peak CK

Type and Site of Infarction	Patients (n)	Time to Peak CK (Hours)
Total population	120	23 ± 1
Transmural	90	25 ± 1
Nontransmural	30	17 ± 2
Anterior transmural	52	23 ± 1
Inferior transmural	38	25 ± 1
Anterior nontransmural	19	18 ± 2
Inferior nontransmural	11	16 ± 2

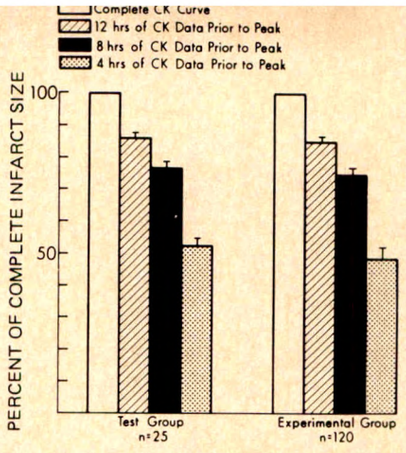


FIGURE 4. The extent of underestimation of MI size for complete and incomplete total CK curves in the test group compared with that observed in the experimental group. As is evident from the bar graph, the percent underestimation of MI size is virtually identical for each interval of data included for the 2 groups.

and the interval of inclusion of data. The figure illustrates that more than half of CK is released before the time of occurrence of peak plasma activity. The standard deviation for the correction factor for the shortest interval of inclusion of data, within 4 hours to peak, is 7%, as opposed to only 1.5% for the interval beginning 10 hours before peak. The rate of release of CK into plasma is slow during the initial 8 to 10 hours, but more rapid as the time to peak is approached. Thus, over the interval of 18 to 24 hours before peak, the curve is relatively flat, with underestimation of MI size based on exclusion of data before this interval consistently in the range of 10%. Inclusion of data beginning 24 hours before peak exhibits virtually the same underestimation and derived correction factor (Table V).

TABLE V Correction Factors

Time From Initial CK Value to Peak Plasma CK	MI Size Based on Incomplete Estimates Expressed as a Percentage of Infarct Size Based on Complete Estimates
2	34
3	43
4	49
5	59
6	65
7	71
8	75
9	79
10	81
11	83
12	85
13	86
14	87
15	88
16	88
17	89
18	89
19	89
20	90

Correction formula: Corrected infarct size = incomplete infarct size % of projected infarct size ×100.

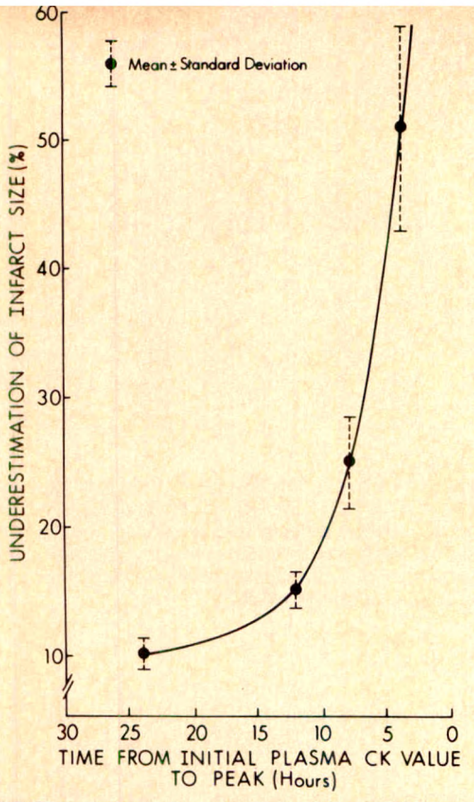


FIGURE 5. The relation between omission of early CK data and estimates of MI size with respect to the ascending plasma CK curve. As is evident from the graph, omission of CK data before 15 hours' peak CK activity has a minimum effect, with an underestimation of MI size of only about 10 to 22%. The effect on estimates increases exponentially as the time to peak decreases. Also shown are the means and standard deviations for each correction factor. The standard deviation does not exceed 7% for any correction factor.

Based on the relation evident in Figure 5, we expressed the percentage of complete estimates of MI size for incomplete estimates as a function of the time of occurrence of peak (Table V). The approach applies to all patients in whom the initially available plasma CK precedes the peak plasma CK activity by at least 2 hours.

With the correction procedure noted in Table V obtained from the experimental group, the estimates in the test group were corrected for 4 to 24 hours of data loss and the results compared with the estimates of MI size based on complete CK curves. Data for each patient are shown in Table VI. The values for corrected, incomplete estimates are very similar to the values estimates from the complete CK curve.

Discussion

In the present study, we have shown that omission or loss of early CK data leads to underestimation of MI size. The extent to which MI size is underestimated depends not only on how much data is missing, but also when acquisition begins with respect to variables of the CK curve. Analysis of the data indicates that approximately two thirds of the CK released into the plasma

TABLE VI Comparison of Estimates of MI Size in the Test Group

Patient	MI Size Estimated From Complete CK Curves	Estimate Based on Data Beginning 24 Hours Before Peak CK		Estimate Based on Data Beginning 12 Hours Before Peak CK		Estimate Based on Data Beginning 8 Hours Before Peak CK		Estimate Based on Data Beginning 4 Hours Before Peak CK	
		U	C	U	C	U	C	U	C
1	16	15	17	14	17	10	13	7	14
2	56	50	55	43	51	38	51	31	62
3	4	4	5	3	4	3	4	2	4
4	56	48	51	39	46	36	48	26	52
5	10	8	9	8	10	8	11	5	10
6	25	21	23	22	26	19	25	14	28
7	131	127	140	110	131	78	104	59	118
8	36	30	33	28	33	32	43	19	38
9	48	40	44	39	46	31	44	24	48
10	68	63	70	59	70	55	73	36	72
11	125	122	132	91	108	84	112	58	116
12	57	55	61	42	50	39	52	27	54
13	29	25	28	24	29	20	27	18	36
14	28	27	30	22	26	20	27	13	26
15	8	8	9	7	8	6	8	4	8
16	8	6	7	7	8	7	9	4	8
17	13	12	13	11	13	9	12	6	12
18	45	38	42	37	44	35	46	22	44
19	114	82	91	85	101	87	116	51	102
20	85	72	80	58	70	47	63	40	80
21	13	13	14	12	14	11	15	7	14
22	36	31	34	26	31	22	29	17	34
23	6	6	7	5	6	4	5	3	6
24	29	22	25	20	24	19	26	14	28
25	4	3	4	3	4	2	3	2	3

C = corrected; U = uncorrected.

appears within 24 hours after the initial CK elevation, corresponding to the mean interval to peak CK (Table VI). The rate of increase of plasma CK activity reflecting the rate of release of CK from the myocardium into the blood is not constant. The pattern of release conforms to a sigmoid curve with initially slow, followed by rapidly increasing release during 15 hours before plasma CK. Thus, in a patient with transmural MI and a representative CK curve with peak activity 24 hours after the onset of symptoms, a lag phase of 4 to 5 hours occurs during which essentially no measurable CK is released into the plasma. Subsequently, a 6- to 8-hour phase of slow release follows. Omission of data during these phases with the initial CK sample obtained 10 to 12 hours after the onset of symptoms results in underestimation of MI size but only by 10 to 12%. After this interval, however, release becomes rapid, and omission of data leads to marked underestimation of MI size.

The consistent pattern of CK release results in a close correlation between complete and incomplete estimates of MI size based on the same interval of data loss. With the use of 24 hours or the time of occurrence of peak CK as a reference point, the correction factors convert incomplete estimates to close approximations of complete ones, for both total and MB CK. Correction is equally applicable to anterior and inferior, transmural and nontransmural MI. The correction factors were derived from 120 patients with MI size ranging from 5 to 140 CK-g-Eq, a range similar to that observed for the MILIS population as a whole. The range of MI size is similar to that observed in 800 other patients admitted to Barnes Hospital before the initiation of the MILIS study. Application of the derived correction factors to a separate test sample corroborated their utility. Thus the present results indicate that if the time of occur rence of peak CK can be determined, MI size can b estimated accurately despite the absence of early CK data. In view of the estimated plasma MB CK half-lif of 6 to 8 hours, a sampling frequency of every 4 hour should be adequate for detection of peak plasma CK Peak plasma CK correlates reasonably well with MI siz but is less accurate than the total integrated release.[2] This is due to the nature of the plasma CK time-activity curve which does not conform to a bell-shaped curve but rather rises to a peak and exhibits a plateau o varying duration during which a significant amount o CK is released which is not reflected by the peak. Th correlation between peak plasma CK and MI size is goo if the plateau phase is of short duration, but is poor i prolonged.[30]

The approach developed provides a means to esti mate MI size in those patients in whom early CK value are missing. Its application should make it possible t obtain estimates of MI size in most patients hospitalize with MI. In the Barnes Hospital Cardiac Care Unit, 93% of patients are admitted before the plasma CK activity has reached a peak. In this MILIS population, 96% o patients are enrolled before the time of occurrence o peak CK. Thus, in clinical trials employing MI size a the endpoint, results from an appreciable number o patients who might otherwise have to be excluded should be available, reducing the total number of pa tients required for achieving desired statistical power In patients undergoing interventions such as strep tokinase-induced reperfusion where the plasma CK curve is significantly altered (namely more rapid releas

f CK), it may be necessary to derive the correction actor from complete curves to compensate for unvailable early values.

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Appendix

Clinical Units

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Core Lab for Creatine Kinase Analysis: Washington University School of Medicine: Robert Roberts, MD, Burton E. Sobel, MD, M. Benjamin Perryman, PhD, Cynthia Ritter, Susan Payne.

Core Lab for Technetium-99m Pyrophosphate Myocardial Scintigram Analysis: University of Texas Health Science Center at Dallas: James T. Willerson, MD, Robert W. Parkey, MD, Samuel E. Lewis, MD, Ernest M. Stokeley, PhD, Irma Dobbins.

Core Lab for Holter Recording Analysis: Washington University School of Medicine: Lewis J. Thomas, Jr., MD, Kenneth W. Clark, Patricia Moore, PhD, J. Phillip Miller.

Core Lab for the Evaluation of Ventricular Function: Massachusetts General Hospital: H. William Strauss, MD, Nathaniel M. Alpert, PhD, Kenneth A. McKusick, MD.

Core Laboratory for Pathology: Duke University Medical Center: Donald B. Hackel, MD, Raymond Ideker, MD, Eileen Mikat, MD, Keith Reimer, MD.

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Serial Exercise Testing Up to 6 Years After Coronary Bypass Surgery: Behavior of Exercise Parameters in Groups With Different Degrees of Revascularization Determined by Postoperative Angiography

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To evaluate the behavior of exercise parameters in patients with different angiographically defined degrees of revascularization, serial exercise tests were analyzed in 435 patients 1 to 6 years after coronary artery bypass grafting (CABG). All patients had undergone postoperative angiography 2 to 12 months after CABG to determine the degree of revascularization achieved. Revascularization was complete in 182 patients (all significantly stenosed arteries had patent grafts), sufficient in 176 patients (at least the dominant artery supplying the left ventricle had a patent graft) and incomplete in 57 patients (the dominant artery supplying the left ventricle had a closed graft). Twenty patients had all grafts occluded. Exercise tolerance, angina-free exercise tolerance (angina threshold), maximal double product, prevalence of ≥0.1 mV exercise-induced S-T segment depression, and the prevalence of the combination of S-T segment depression plus angina pectoris were determined in serial exercise tests (average of 3.0 postoperative exercise tests per patient for a mean follow up of 3.5 years). Patients with complete, sufficient, and incomplete revascularization showed improvement of all exercise parameters for 6, 4, and 1 year after CABG, respectively. Patients with all grafts occluded had improvement of only some exercise parameters.

Five years after CABG, exercise tolerance was improved by 24 W ($p < 0.0005$) and 21 W ($p < 0.005$) in patients with complete and sufficient revascularization, respectively, and not improved in patients with incomplete revascularization or with all grafts occluded. The angiographically determined completeness of revascularization correlates with the extent and the duration of improvement of exercise parameters after CABG.

The improvement of effort angina in a large percentage of patients is well established at 6 to 12 months after coronary artery bypass grafting (CABG).[1–5] Relief of angina pectoris is associated with improvement in exercise tolerance and a change in the functional class according to the New York Heart Association classification as applied to angina by the Canadian Cardiovascular Society.[6] Although the grading according to the New York Heart Association classification is convenient, there is significant room for subjective interpretation of complaints by the patients and the physician. Exercise testing can provide more objective information on the physiologic state of the cardiovascular system after CABG, particularly when used in serial evaluation of patients after CABG. Few data are available on the results of serial exercise testing after CABG,[1,7,8] and there have been no studies reported on serial exercise testing in patients with different degrees of revascularization. The present study describes the results of serial exercise testing up to 6 years after CABG in patients with angiographically defined degrees of revascularization.

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Methods

Patients: Included in this study are patients who fulfilled the following criteria: (1) bypass surgery performed at age ≤55 years without associated procedures; (2) postoperative angi-

TABLE I Patient Characteristics in the Total Group and the 4 Subgroups With Angiographically Determined Different Degrees of Revascularization

	Total Group	Subgroups			
		I	II	III	IV
Patients (n)	435	182	176	57	20
Male/female	420/15	174/8	171/5	55/2	20/0
Mean age at surgery (yr ± SD)	48 ± 4	48 ± 5	48 ± 5	49 ± 5	48 ± 4
Vessels diseased (n)	2.45	2.27	2.64	2.70	2.05
Distal anastomoses per patient	2.52	2.31	2.73	2.73	2.35
Patent anastomoses per patient	1.92	2.31	2.04	1.28	0
Patent anastomoses per diseased vessel	0.80	1.02	0.77	0.47	0

SD = standard deviation.

ographic evaluation of graft patency and determination of the degree of revascularization performed according to the criteria pointed out later; and (3) preoperative and postoperative exercise testing performed. Patients included in this study are not part of a randomized study.

CABG was performed after an intense trial of medical management under hospital conditions was unsuccessful in reducing anginal symptoms to an acceptable degree. Medical management (aside from vigorous efforts to eliminate risk factors) consisted of therapy with a combination of long-acting nitrates, a beta-blocking agent and a calcium antagonist, usually nifedipine.

Most patients had not been working for several months before CABG because of limiting symptoms or because of recent myocardial infarction with persisting angina. Angiography after CABG was offered to every patient during the study period; patients included in the study comprised 77% of all those under age 56 who underwent operation during the study period. Patients not included are those who refused postoperative angiographic evaluation, or those in whom exercise testing was not performed for a variety of reasons before or 1 year after surgery.

Angiographic Evaluation

Preoperative coronary angiography was performed using the Sones technique in the majority of patients (95%) and the Judkins technique in the remainder after sublingual nitroglycerin had been given. Angled caudocranial views were used routinely from 1974 on. Lesions in the coronary arteries were analyzed by measuring the reduction in luminal diameter. Postoperative angiography was performed using the Judkins technique in most patients (75%) and the Sones technique in the remaining patients. A vessel was considered adequately revascularized if the bypass showed no narrowing >50% of the luminal diameter of the grafted artery and if the grafted artery had no distal lesions of >50% luminal diameter reduction. Patients were classified into 4 groups according to the degree of revascularization as determined by postoperative angiography.

Definition of different degrees of revascularization: *Group I: Complete revascularization:* All significantly stenosed bypassable arteries were provided with an open graft: Bypassable diagonal branches of the left anterior descending artery and marginal or posterolateral branches of the circumflex artery and posterolateral branches of the right coronary artery also were considered if appropriate in size (that is, >1.2 mm). A graft was considered open if the luminal diameter of the graft was narrowed to no more than 50% of the luminal diameter of the grafted artery.

Group II: Sufficient revascularization: At least the bypass to the dominant vessel supplying the left ventricle was provided with an open graft. The vessel supplying the major portion of the left ventricle was considered the dominant vessel; this was the left anterior descending artery in most patients. Occasionally, an exceptionally large right coronary or circumflex artery could supply the major portion of the left ventricle (as estimated by the angiographer) and was considered the dominant vessel. A further bypass may be occluded or a significantly stenosed bypassable vessel was left ungrafted.

Group III: Incomplete revascularization: The dominant vessel supplying the left ventricle was significantly stenosed and the graft stenosed or occluded. At least one additional bypass was patent.

Group IV: All grafts were occluded.

Exercise Testing

All patients had undergone exercise testing before and 1 year after CABG. Thereafter exercise tests were scheduled at yearly intervals at the anniversary of the operation. All exercise tests were performed with an electrically braked bicycle ergometer (Siemens-Elema) with the patient in the supine position. A 12-lead electrocardiogram and blood pressure were recorded at rest and at 2-minute intervals. Exercise was begun with 25 or 50 W and the work load was increased every 2 minutes by 25 or 50 W until fatigue, severe dyspnea, angina pectoris, and ≥0.4 mV S-T segment depression occurred or 80% of the age predicted maximal heart rate was reached. The following features were analyzed: exercise tolerance, angina-free exercise tolerance (in watts [angina threshold]), maximal S-T segment depression, occurrence of angina pectoris, and the peak heart rate-blood pressure product (mm Hg × beats/min).

Statistical Analysis

The difference between pre- and postoperative exercise parameters was analyzed for statistical significance using Student's paired *t* test. The difference in the pre- and postoperative prevalence of ≥0.1 mV exercise-induced S-T segment depression and S-T segment depression plus angina pectoris was tested by chi-square analysis using contingency tables.

Results

Angiography: Four hundred thirty-five patients (420 men and 15 women) with a mean age of 48 years at the time of CABG were included in the study. Postoperative angiography was performed 8 weeks after surgery in 87 patients (20%) and 1 year after surgery in 348 patients (80%). Revascularization was complete in 182 patients, sufficient in 176, and incomplete in 57. Twenty patients had all grafts occluded. The mean number of

TABLE II Number and Percentage of Patients Who Returned at the Indicated Follow-Up Interval for Repeat Exercise Testing

	Preoperative	Years After Surgery					
		1	2	3	4	5	6
Patients (n) alive at follow-up interval	435	435	435	433	372	266	159
Patients (n) with exercise ECG	435	435	349	286	236	107	78
Patients (%) with exercise ECG at follow-up interval	100	100	80	66	63	40	49

ECG = electrocardiography.

TABLE III Exercise Tolerance (W) in the Supine Position

Degree of Revascularization	Preoperative	Years Postoperatively					
		1	2	3	4	5	6
Complete	65 ± 37 (182)	103 ± 34* (182)	95 ± 37* (155)	95 ± 39* (125)	91 ± 40* (113)	89 ± 46* (61)	95 ± 43† (49)
Sufficient	59 ± 31 (176)	96 ± 33* (176)	86 ± 36* (135)	82 ± 32* (116)	81 ± 30* (92)	80 ± 35† (33)	86 ± 35† (22)
Incomplete	62 ± 31 (57)	85 ± 28* (57)	76 ± 35‡ (45)	76 ± 37‡ (39)	78 ± 43§ (25)	61 ± 51§ (7)	88 ± 66§ (7)
All grafts occluded	67 ± 31 (20)	81 ± 37§ (20)	75 ± 40§ (14)	101 ± 32§ (6)	89 ± 45§ (6)	85 ± 36§ (6)	

All values are mean ± 1 standard deviation. Numbers in parentheses represent number of patients examined.
All p values are comparisons with preoperative values: * $p < 0.0005$; † $p < 0.005$; ‡ $p < 0.05$; § not significant ($p > 0.05$).

TABLE IV Angina-Free Exercise Tolerance (W) in the Supine Position

Degree of Revascularization	Preoperative	Years Postoperatively					
		1	2	3	4	5	6
Complete	43 ± 36 (182)	96 ± 42* (182)	83 ± 47* (155)	79 ± 51* (125)	70 ± 52* (113)	70 ± 55† (61)	75 ± 55† (49)
Sufficient	36 ± 30 (176)	85 ± 42* (176)	72 ± 44* (135)	62 ± 44† (116)	58 ± 40† (92)	61 ± 45† (33)	73 ± 44† (22)
Incomplete	41 ± 31 (57)	67 ± 36* (57)	56 ± 43† (45)	54 ± 47§ (39)	62 ± 53‡ (25)	43 ± 60§ (7)	66 ± 77§ (7)
All grafts occluded	40 ± 39 (20)	70 ± 42† (20)	58 ± 46§ (14)	90 ± 42§ (6)	76 ± 41§ (6)	76 ± 47§ (6)	

All values are mean ± 1 standard deviation. Numbers in parentheses represent number of patients examined.
All p values are comparisons with preoperative values: * $p < 0.0005$; † $p < 0.005$; ‡ $p < 0.05$; § not significant ($p > 0.05$).

diseased vessels, constructed anastomoses, patent distal anastomoses per patient, and the mean number of patent distal anastomoses per diseased vessel in the 4 groups are shown in Table I.

Exercise testing and follow-up: All patients had undergone exercise testing before and 1 year after CABG; most patients returned each year for routine exercise testing. For a mean follow-up time of 3.5 years, a mean number of 3.0 exercise tests per patient were available for review. The percentage of patients who returned at the indicated follow-up interval is shown in Table II. The results of preoperative and postoperative exercise testing in the 4 groups with respect to the different exercise variables are shown in Tables III to VI and Figure 1.

Exercise tolerance (Table III): Exercise tolerance was significantly increased 1 year after CABG in Groups I to III but not in Group IV. The gain in exercise tolerance was similar in Groups I and II 1 year after CABG but smaller in Group III. There was a slow but gradual decline of exercise tolerance with time: 4 years after CABG only the condition of patients in Groups I and II was improved and continued to improve up to 6 years, whereas patients in Group III failed to show significant improvement 4 to 6 years after surgery. Patients with all grafts occluded showed no significant improvement in exercise tolerance.

Angina-free exercise tolerance (angina threshold) (Table IV): The relief of angina pectoris after CABG was reflected in a higher exercise load that could be performed without the occurrence of angina. At 1 year after CABG, angina-free exercise tolerance was improved in all 4 subgroups; again patients in Groups I and II continued to have improved angina-free exercise tolerance up to 6 years after surgery, whereas in those in Groups III and IV the effect of CABG on exercise tolerance was no longer significant at 3 years and 2 years, respectively.

S-T segment depression (Table V): Before CABG >75% of patients had ≥0.1 mV S-T segment depression

TABLE V Prevalence of S-T Segment Depression During Exercise

Degree of Revascularization	Preoperative	Years Postoperatively 1	2	3	4	5	6
Complete	76 (138/182)	20* (36/182)	22* (34/155)	20* (25/125)	27* (30/113)	34* (21/61)	33* (16/49)
Sufficient	78 (137/176)	29* (52/176)	32* (44/135)	34* (40/116)	36* (33/92)	42* (14/33)	63 (14/22)
Incomplete	77 (44/57)	47† (27/57)	56‡ (25/45)	44† (17/39)	56§ (14/25)	43§ (3/7)	71§ (5/7)
All grafts occluded	85 (17/20)	35† (7/20)	21* (3/14)	17† (1/6)	50§ (3/6)	33‡ (2/6)	

Values represent percentages of patients with ≥0.1m S-T segment depression during exercise. Numbers in parentheses represent number of patients with S-T segment depression/number of patients examined.
All p values are comparisons with preoperative values: * $p < 0.0005$; † $p < 0.005$; ‡ $p < 0.05$; § not significant ($p > 0.05$).

TABLE VI Maximal Double Product (HR × mm Hg × min^{-1} × 10^{-2})

Degree of Revascularization	Preoperative	Years Postoperatively 1	2	3	4	5	6
Complete	193 ± 56 (182)	250 ± 71* (182)	259 ± 67* (155)	245 ± 75* (125)	241 ± 67* (113)	241 ± 70† (61)	236 ± 67‡ (49)
Sufficient	176 ± 47 (176)	235 ± 69* (176)	239 ± 63* (135)	241 ± 62* (116)	232 ± 57* (92)	219 ± 61† (33)	247 ± 75† (22)
Incomplete	186 ± 50 (57)	213 ± 53† (57)	219 ± 49† (45)	213 ± 45‡ (39)	202 ± 50§ (25)	199 ± 57§ (7)	226 ± 72§ (7)
All grafts occluded	194 ± 56 (20)	230 ± 80§ (20)	226 ± 56‡ (14)	237 ± 71§ (6)	232 ± 89§ (6)	221 ± 58§ (6)	

All values are mm Hg × min^{-1} × 10^{-2} ± 1 standard deviation. Numbers in parentheses represent number of patients examined.
All p values are comparisons with preoperative values: * $p < 0.0005$; † $p < 0.005$; ‡ $p < 0.05$; § not significant ($p > 0.05$).

during exercise. Patients in all 4 groups improved after CABG; those who had undergone complete revascularization benefited most. Also, patients with all grafts occluded had less S-T segment depression after CABG. There was slow and progressive loss in improvement for all revascularization groups. Six years after surgery, only patients with complete revascularization had significantly less S-T segment depression than before surgery; also, the small number of patients with all grafts occluded had less S-T segment depression 5 years after surgery than before CABG.

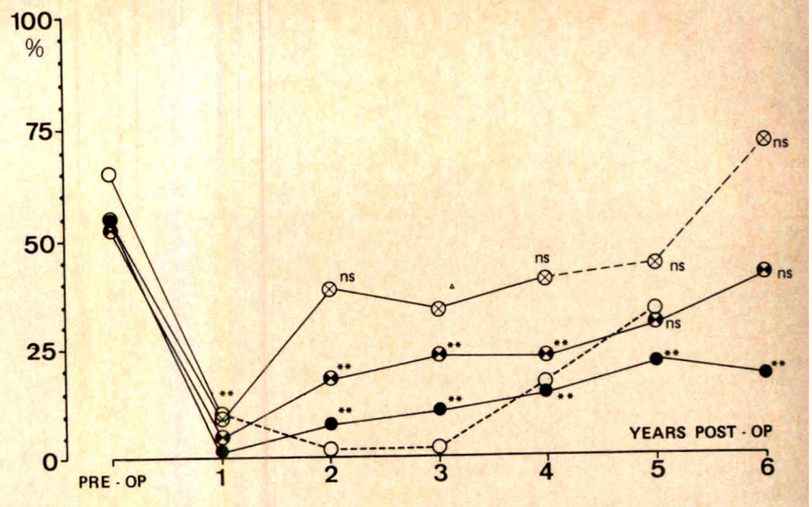
S-T segment depression and angina pectoris (Fig. 1): The occurrence of both S-T segment depression and angina pectoris during exercise testing can be considered a more reliable indicator of ischemia than either parameter alone.[9] All 4 groups benefited significantly with respect to the occurrence of angina pectoris and S-T segment depression at 1 year after CABG. At 2 years, in patients with incomplete revascularization, the prevalence of these combined parameters no longer differed from the prevalence before operation. Only patients with complete revascularization showed a highly significant lower prevalence of angina and S-T segment depression up to 6 years after CABG. The increase in prevalence of these combined parameters was 3% per year in patients with complete revascularization, approximately 6% in patients with sufficient revascularization, and approximately 10% in patients with incomplete revascularization.

Maximal double product (Table VI): The maximal product of heart rate and systolic blood pressure (maximal double product) that can be achieved during exercise correlates with myocardial oxygen supply during exercise.[10] The maximal double product achieved during exercise after CABG increased significantly in Groups I to III. The increase of the double product was similar in Groups I and II, and less marked in Group III. Patients with complete failure of the operation did not show a significant increase of the double product during exercise at 1 year after CABG. In Group III, the maximal double product was no longer improved at 4 years after surgery, whereas patients in Groups I and II showed significant improvement up to 6 years after surgery.

Analysis of all exercise parameters (Fig. 2): Patients with complete revascularization showed significant improvement in all 5 parameters up to 6 years after CABG (Fig. 2). Patients with sufficient revascularization showed significant improvement in all parameters up to 4 years after surgery, whereas those with incomplete revascularization showed improvement of all parameters only 1 year after CABG. Patients in whom there was complete failure of the operation showed improvement in only some exercise parameters at 1 year after surgery.

Discussion

In serial exercise testing improved exercise performance was demonstrated up to 1.5,[11] 2,[12] 3.5,[1] and 4 years[7] after CABG. Recently, improved exercise performance lasting up to 5 years after CABG was reported in a larger number of patients.[8] Postoperative angiographic evaluation of patients after CABG has demonstrated that the completeness of revascularization



DEGREE of REVASCULARIZATION							n = No. of exercised patients
● Complete	n = 182	182	155	125	113	61	49
⊗ Sufficient	n = 176	176	135	116	92	33	22
⊗ Incomplete	n = 57	57	45	39	25	7	7
○ All gr. occl.	n = 20	20	14	6	6	6	

** $p < 0.0005$ * $p < 0.005$ ^ $p < 0.05$ ns = $p > 0.05$

FIGURE 1. Prevalence of exercise-induced angina pectoris in combination with exercise-induced S-T segment depression in the 4 groups before and 1 to 6 years after CABG. All groups were improved 1 year after CABG; the annual recurrence rate of this combined parameter is 3% for patients with complete revascularization, 6% for those with sufficient revascularization, and approximately 10% for those with incomplete revascularization. Only patients with complete revascularization showed significant improvement up to 6 years postoperatively (POST-OP). All p values compared with preoperative (PRE-OP) results. gr. occl. = graft occlusion; ns = not significant.

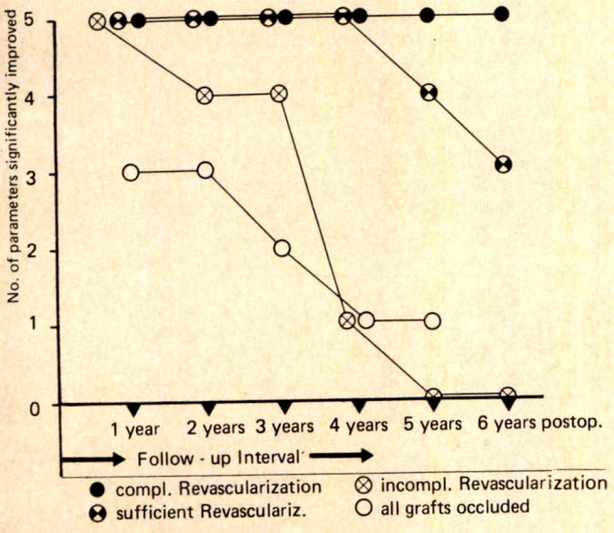


FIGURE 2. Summary of results of Tables III to VI and Figure 1. Illustrated are the number of examined parameters that were significantly improved at 1 to 6 years after surgery in comparison with preoperative parameters. Only patients with complete (compl.) revascularization had improvement in all exercise parameters up to 6 years after surgery. Exercise parameters examined were exercise tolerance, angina-free exercise tolerance (angina threshold), prevalence of ≥0.1 mV S-T segment depression, prevalence of S-T segment depression plus angina pectoris, and maximal double product of heart rate and systolic blood pressure.

correlates with the degree of symptomatic improvement as evaluated by the classification of the New York Heart Association and also with the extent of early[4,13] and late[14,15] functional improvement after CABG as well as with improvement in exercise hemodynamic variables.[16] Siegel et al[13] reported on 128 patients who underwent postoperative angiographic evaluation between 2 and 29 months after CABG. Eleven patients with partial or complete graft failure had no significant improvement in most exercise parameters, whereas patients with complete revascularization had significant improvement in all exercise parameters 2 to 29 months after CABG. Lawrie et al[15] reexamined 51 patients more than 5 years after CABG with angiographic reevaluation and noted a better exercise performance with respect to the occurrence of chest pain, S-T segment depression, exercise duration, maximal heart rate, and maximal double product in patients who had no residual lesions compared with those who had 1 or 2 residual lesions. However, no preoperative comparisons were available and no statistical analysis was performed. There are, however, no prospective data available on the duration of functional improvement measured with exercise testing in angiographically defined subsets of patients with different degrees of revascularization.

Most of the studies dealing with the long-term effect of CABG on improvement in functional class or in exercise tolerance were performed in patients operated on in the early 1970s with mostly incomplete revascularization and a lower graft patency rate than that accomplished in recent years. Therefore, results after CABG obtained today may be superior to those obtained in the early 1970s.[17] The prevalence of S-T segment depression with angina pectoris at low levels of exercise (≤50 W) was recently reported to be as low as 10% at 5 years after CABG.[18]

Our results indicate that patients with complete revascularization—as determined by postoperative angiography—had an excellent result with respect to all examined parameters at 1 year after surgery. This is in agreement with previous reports.[1,13,14] The improvement in the parameters of exercise performance is maintained up to 6 years after CABG. Thus, although CABG is a palliative procedure, there was only slow loss in improvement over the years, and the new occurrence

of S-T segment depression with exercise-induced angina was approximately 3% per year in this subgroup. The occurrence of new symptoms can be attributed to a graft occlusion rate of 2% per year after the first year and to progression of disease in the native coronary arteries.[19–21] Because sequential angiography was not performed, the contribution of each individual component cannot be assessed in these patients.

Patients with sufficient revascularization also had significant improvement in all exercise parameters at 1 year after CABG (to a slightly lesser extent than in the group with complete revascularization). Furthermore, the improvement in all exercise parameters lasted only up to 4 years after CABG.

At 5 years the prevalence of exercise-induced angina pectoris combined with S-T segment depression was no longer different from the preoperative prevalence; however, the angina-free exercise tolerance (angina threshold) was still significantly greater than before CABG. Thus, despite a similar occurrence of S-T segment depression associated with angina pectoris at 5 years after surgery, this group was able to perform a greater work load without occurrence of angina pectoris than before surgery, and therefore still had significant benefit from the operation. This example illustrates that it is necessary to consider more than only a single parameter (that is, S-T segment depression) in the evaluation of postoperative exercise testing.

In Group III the 1-year postoperative improvement of exercise performance was markedly less than in patients with complete revascularization: The exercise tolerance, the angina-free exercise tolerance, and the maximal double product were significantly lower than in the group with complete revascularization. The steep increase in the prevalence of S-T depression plus angina between 1 and 2 years might be explained by partial denervation at 1 year, because the prevalence of S-T depression is high but patients do not experience angina.

Patients with all grafts occluded showed improvement in only some parameters 1 year after CABG. Remarkable is the absence of angina and S-T segment depression during exercise. However, exercise tolerance and maximal double product were not improved. Similar results were reported by Block et al[22] in patients who underwent unsuccessful revascularization.

In conclusion, in our study correlations between angiographically defined degrees of revascularization and the long-term effect of CABG on exercise performance could be demonstrated. The long-term outlook for patients in whom complete revascularization has been achieved is excellent. Patients with lesser degrees of revascularization have not only less improvement after surgery, but also a higher rate of recurrence of symptoms during the follow-up years.

Limitations of the study: Although the mean number of grafts placed in the patients included in this study is smaller than the number of grafts placed today in our institution, the assessment of the degree of revascularization achieved during surgery has not changed much during recent years. A major change has taken place in patient selection: patients who would have been denied surgery at the time of this study can undergo successful CABG today with up to 8 and more distal anastomoses by sequential graft technique.[23] However, long-term results in patients with multiple distal anastomoses by sequential graft technique are still pending.

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Cardiokymography During Exercise Testing: A New Device For the Detection of Coronary Artery Disease and Left Ventricular Wall Motion Abnormalities

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The cardiokymograph (CKG) is a device that has been shown to reflect left ventricular (LV) wall motion abnormalities. Its accuracy in detecting coronary artery disease (CAD) during treadmill exercise testing was assessed in 204 consecutive patients undergoing coronary arteriography. Of the 188 patients with a technically adequate CKG, 146 (78%) had significant CAD. The sensitivity and specificity were similar for both the exercise electrocardiogram (ECG) (66% and 86%, respectively) and the exercise CKG (73% and 95%, respectively). An abnormal exercise CKG was significantly more common in patients with 3-vessel CAD than in those with 1-vessel disease (97% versus 52%, respectively; p <0.001) and in patients with left anterior descending disease than in those without (85% versus 26%, respectively; p <0.001). Seventy patients showed both an abnormal exercise ECG and CKG; all had CAD and 86% had multivessel CAD. Forty-eight patients demonstrated a normal exercise ECG and CKG; 29% had CAD but only 6% had multivessel CAD. Among 55 patients who had simultaneous exercise radionuclide ventriculography, new septal or apical wall motion abnormalities were found in 79% (23 of 29) of patients with an abnormal CKG compared with 19% (5 of 26) of patients with a normal CKG (p <0.001). Thus, the CKG during exercise testing accurately reflects LV wall motion abnormalities and can be used to improve the diagnostic accuracy of exercise testing as an additional marker of myocardial ischemia.

The diagnosis of coronary artery disease (CAD) may be difficult to ascertain on the basis of the history, physical examination, and resting electrocardiogram (ECG). Even the standard exercise test has diagnostic limitations for the detection of CAD because of poor sensitivity or specificity in different population groups.[1–3] For these reasons, other noninvasive tests have been used to aid in the diagnostic evaluation of CAD, such as exercise thallium[4,5] or radionuclide ventriculography[6,7]; however, these studies are expensive, require complex equipment, and entail the risk, albeit small, of radiation exposure.

The cardiokymograph (CKG) offers an additional independent marker of myocardial ischemia.[8–11] It is a relatively simple device that has been shown experimentally to accurately detect regional wall motion by recording tissue movements through changes in an electromagnetic field, and it can be recorded at rest and shortly after exercise. In 1 previous clinical study by the investigators who initially described the device,[12] the sensitivity and specificity of the exercise CKG was significantly better than that obtained with exercise ECG.[13] This investigation further analyzes the diagnostic accuracy of the CKG performed in conjunction with exercise testing. A subgroup of patients additionally underwent exercise radionuclide ventriculography to correlate left ventricular (LV) wall motion during exercise recorded by the CKG with that detected by radionuclide ventriculography.

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Methods

Patients: During an 18 month period, 204 consecutive patients (175 men and 29 women) with a mean age of 53 ± 7 years (range 31 to 75) without prior cardiac surgery were referred for cardiac catheterization because of suspected or known CAD and were able to undergo exercise testing. The decision to perform cardiac catheterization was made by the patient's attending physician before the exercise test which was performed 1 day before catheterization. The chest pain com-

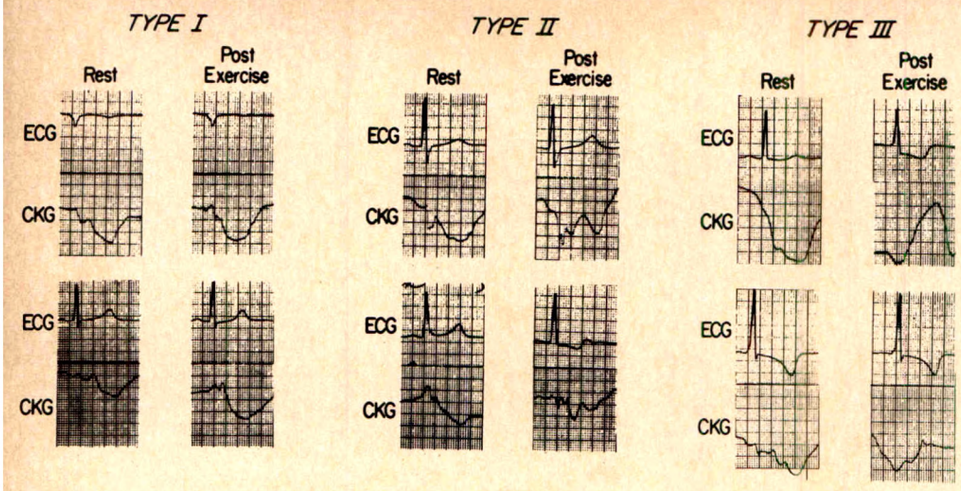

FIGURE 1. Two examples each of the 3 types of cardiokymographic patterns at rest and 2 to 3 minutes after exercise: Type I, the normal response, demonstrated inward systolic motion; Type II, an abnormal response, consisted of a paradoxical outward systolic movement postexercise after an initial early inward motion; and Type III, an abnormal response, exhibited total outward systolic motion postexercise. CKG = cardiokymography; ECG = electrocardiography.

plaints of the patients were categorized into 1 of 3 groups before catheterization: typical angina (64%), atypical angina (19%), and nonischemic chest pain (12%). Six percent of the patients were asymptomatic after a myocardial infarction.

Cardiokymography: Each patient had a CKG at rest and during recovery from exercise. The electronic features of the CKG have been previously described in detail.[8–14] In brief, the CKG (Cardiokinetics, Seattle, Washington) consists of a circular, flat capacitive plate which is mounted in a plastic ring and strapped to the chest. Tissue motion beneath the plate distorts an induced electromagnetic field which in turn alters the frequency of an external oscillator. This change in frequency is converted into a change in voltage proportional to the original motion, which is then amplified and displayed on a multichannel recorder as a continuous analog signal. The frequency response of the system is flat ±10% from 0.1 to 90 Hz.[14]

The CKG tracing was initially recorded in the supine position at end-expiration with the ring placed over the precordium between ECG positions V_2 to V_5, and a transthoracic ECG lead was recorded simultaneously at a paper speed of 50 mm/s. The optimal position for the most accurate CKG tracing was marked on the chest (most commonly obtained in the V_3 position). Within 2 to 3 minutes after cessation of exercise, a CKG tracing was again obtained using the same position at end-expiration as previously recorded at rest, and was then repeated at least once more during the recovery period.

The CKG tracings were interpreted by 3 independent readers who had no prior knowledge of the results of the exercise ECG or coronary arteriogram. Two readers interpreted all the CKG tracings on separate occasions, at least 2 weeks apart. The tracings were classified according to 3 patterns (Fig. 1) as previously described by Silverberg et al[13]: *Type I*, the normal pattern, was characterized by an initial upward systolic preejection movement followed by a downward motion during ejection, representing inward motion of the LV wall. The *Type II* pattern consisted of a paradoxical systolic outward motion with an amplitude ≥50% of the initial inward motion during early systole. *Type III* motion demonstrated total outward motion during systole without any inward motion. The CKG tracings were considered abnormal if a Type I motion at rest became Type II or III after exercise or a Type II response at rest became Type III after exercise and then returned to the control tracing during recovery.

Exercise test: All patients underwent a symptom-limited, maximal treadmill exercise test according to the standard Bruce protocol.[15] A 12-lead ECG and blood pressure were recorded at rest and during each stage of exercise and recovery. An abnormal electrocardiographic response was defined as the appearance of 1 mm of horizontal or downsloping S-T segment depression or 1.5 mm of upsloping S-T segment depression 80 ms after the J point for 3 consecutive beats during exercise or recovery compared with the upright tracing. If the resting ECG showed S-T segment depression, an additional 1 mm of depression was required.

Exercise radionuclide ventriculography: Fifty-five patients, randomly selected, underwent supine exercise radionuclide ventriculography on the same day as the treadmill exercise test. Radionuclide ventriculography was performed after labelling of red blood cells with technetium-99 sodium pertechnetate according to the technique previously described.[6]

Regional LV function was assessed by analysis of wall motion using both the cinematic display of the average cycle and the static display of the superimposed end-diastolic and end-systolic perimeters. Wall motion was categorized either as normal, hypokinetic, akinetic, or dyskinetic. Abnormal wall motion during exercise was defined as a new hypokinetic, akinetic, or dyskinetic motion involving the apical or septal walls. If the wall motion was abnormal at rest, a positive exercise response consisted of worsening of these abnormalities (hypokinetic to akinetic or akinetic to dyskinetic).

Coronary arteriography: Selective coronary arteriograms using the brachial or femoral techniques were recorded in multiple projections. Significant CAD was judged present if ≥50% reduction in vessel diameter occurred in the left main coronary artery or a ≥70% narrowing was present in ≥1 of the other major arterial segments. Of the 204 patients, 78% had significant CAD. One-, 2-, and 3-vessel disease was found in 57 patients (28%), 63 patients (31%), and 39 patients (19%), respectively.

Statistical analysis: All analyses of data were performed using chi-square analysis with Fisher's exact test utilized for small sample sizes. Probabilities were considered significant at the 0.05 level.

Results

Technically adequate CKG tracings were obtained in 92% of the 204 patients. Among the 16 patients with inadequate tracings, 12 had a history of myocardial infarction, 11 were classified as having typical angina, and 8 had multivessel CAD.

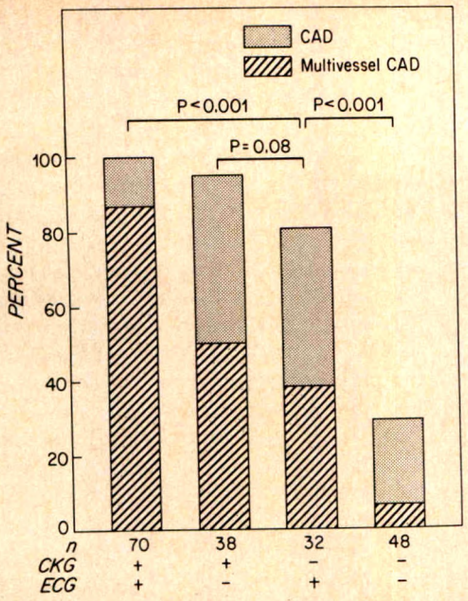

FIGURE 2. Correlation between the combined stress test cardiokymographic and electrocardiographic results and the presence of CAD and multivessel disease. CAD = coronary artery disease; CKG = cardiokymography; ECG = electrocardiography.

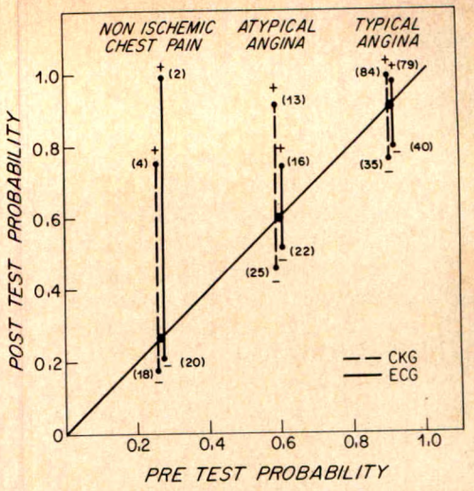

FIGURE 3. The probability of coronary artery disease before and after a positive or negative cardiokymographic (**dashed lines**) or electrocardiographic (**solid lines**) response. The **numbers in parentheses** refer to the number of patients with a given test result in the specific symptomatic subgroup listed at top of the figure. CKG = cardiokymography; ECG = electrocardiography.

Inter- and intraobserver variability: All 3 readers of the CKG tracings were in complete agreement 78% of the time. The discordant interpretations were resolved by group review. Intraobserver variability was found in 9% of the interpretations by 1 reader and 8% by the second reader.

Sensitivity and specificity: Of the 188 patients with technically adequate CKG tracings, 146 (78%) had significant CAD. The CKG stress test was abnormal in 106 patients (sensitivity 73%) while the ECG stress test was abnormal in 96 patients (sensitivity 66%, p not significant [NS]). There were 56 Type II responses and 50 Type III responses after exercise among the 106 abnormal CKG tracings. Either an abnormal CKG or ECG stress test response was present in 90% of the patients ($p < 0.001$, compared with the sensitivity of either the ECG or CKG test alone). In the 14 patients with CAD, whose CKG and ECG stress tests were normal, 10 (71%) failed to reach at least 85% of the age-predicted maximum heart rate, and 11 (79%) had single-vessel CAD.

Of the 188 patients, 42 (22%) had no significant CAD. The CKG stress test was negative in 40 patients (specificity 95%), the ECG stress test was negative in 36 patients (specificity 86%, p = NS), and both stress tests were negative in 34 patients (specificity 81%). Both patients with false-positive CKG stress tests had Type II responses.

Influence of the extent and distribution of CAD: The CKG stress test was abnormal in 52% of patients with 1-vessel CAD, 76% of patients with 2-vessel CAD, and 97% of patients with 3-vessel CAD ($p < 0.001$). The stress test CKG was more sensitive in detecting patients with 3-vessel CAD than was the ECG (97% versus 78%, respectively; $p < 0.01$).

One-hundred patients had significant disease of the left anterior descending coronary artery. The CKG was abnormal in 85% of these patients, compared with 26% of the 88 patients without significant left anterior descending coronary narrowing ($p < 0.001$).

Correlation between the combined test results and CAD (Fig. 2): One-hundred eighteen patients (63%) had concordant results for the CKG and ECG stress tests (70 positive, 48 negative). CAD and multivessel disease were present in 100 and 86%, respectively, of the patients with concordantly positive results compared with 29 and 6%, respectively, of the patients

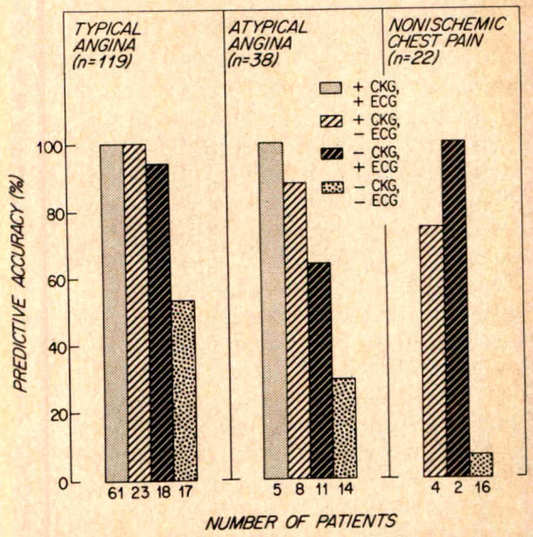

FIGURE 4. Predictive accuracy of concordant or discordant test results in patient subgroups according to symptomatic status. CKG = cardiokymography; ECG = electrocardiography.

with concordantly negative results ($p < 0.001$). When the results of the 2 stress tests were discordant, 62 (89%) of the 70 patients had CAD, and multivessel disease was present in 44%. The predictive accuracy of discordant results for CAD was slightly but not significantly greater for a positive CKG response than for a positive ECG result (95 versus 81%, respectively; $p = 0.08$).

Influence of symptoms and disease prevalence on the accuracy of individual (Fig. 3) and combined (Fig. 4) test results: A history of typical angina pectoris was highly predictive (92%) of the presence of significant CAD. A positive CKG response slightly increased (100%) the probability of CAD. A negative test result, however, was still associated with a high likelihood of CAD in this group of patients (80% for the ECG, 74% for the CKG [Fig. 3], and 53% for concordantly negative tests [Fig. 4]).

In the group classified as having atypical angina, 23 of the 38 patients (60%) were found to have significant CAD. The likelihood of having CAD increased to 92% when the CKG stress test was abnormal (Fig. 3) and 100% when both tests were abnormal. Concordantly negative results were associated with a 29% probability of CAD but only a 7% probability of multivessel disease (Fig. 4).

In the group with nonischemic chest pain, 6 of the 22 patients (27%) had CAD. Six of the patients had either an abnormal CKG or ECG stress test and 1 of the 6 had a false-positive result. Only 1 (6%) of 16 patients with concordantly negative results had CAD in 1 vessel (Fig. 4).

Correlation between cardiokymographic stress test and exercise radionuclide ventriculography: Of the 55 patients tested, 25 had new septal or apical wall motion abnormalities during exercise radionuclide ventriculography and 3 had worsening of preexisting abnormalities. These abnormalities were seen more frequently in the patients with an abnormal CKG stress test (79%, 23 of 29) than in those with negative CKG stress tests (19%, 5 of 26; $p < 0.001$).

Discussion

This study confirms the findings of the 1 previous clinical investigation that stress test cardiokymography is a useful method for detecting myocardial ischemia.[13] The sensitivity and specificity in this consecutive series of patients referred for cardiac catheterization were slightly better than that of exercise electrocardiography and comparable to the results in previous studies analyzing stress test thallium[4,5] or exercise radionuclide ventriculography.[16,17] Its relative simplicity and lack of radiation risk, moreover, makes the CKG an attractive addition to be used in conjunction with the standard exercise test for diagnostic evaluation.

The CKG has been shown experimentally to detect regional wall motion abnormalities[11] which often occur as the initial manifestation of CAD[18] preceding either metabolic[19] or ECG S-T segment abnormalities.[20] This investigation confirms these experimental findings by illustrating that most (79%) patients with abnormal CKG stress tests also demonstrate abnormal LV contraction patterns as determined by exercise radionuclide ventriculography. Since the left anterior descending coronary artery supplies the major portion of the anterior wall, it is not surprising that 85% of patients with abnormal CKG stress tests also had significant left anterior descending narrowing.

Myocardial ischemia during exercise may cause either electrical or mechanical abnormalities. Since the exercise ECG and CKG may detect these different manifestations, analysis of the combined test results should enhance the diagnostic accuracy of either test result alone. When concordantly positive test results were observed, 100% of patients were correctly identified as having CAD, and in 86%, multivessel disease was found. Although concordantly negative results did not entirely eliminate the probability of CAD (29%), the likelihood of finding multivessel disease was extremely low (6%). Two points regarding the 29% prevalence of false-negative responses should be emphasized. First, 10 of the 14 patients with concordantly negative results did not achieve 85% of the maximally predicted heart rate. If these patients were eliminated, only 8% of concordantly negative responders had CAD. Second, our patient population was referred for cardiac catheterization and had a high pretest risk of CAD (78%). In other groups of patients with a lower pretest risk, concordantly negative results would likely yield a lower post-test likelihood of CAD.

Recent studies have emphasized that the results of any noninvasive test used for the detection of CAD depend not only on the sensitivity and specificity of the test result but also on the pretest likelihood of disease in the patient group tested according to Bayesian theorem.[3,21–23] Our investigation supports these conclusions. In the patients with a history of typical angina, a positive stress test ECG or CKG only slightly increased a high pretest risk. Negative combined test results would likely indicate 0- (47%) or 1-vessel (41%) CAD. In the patients with atypical chest pain (the groups classified as having either atypical angina or nonischemic chest pain), a positive CKG stress test alone raised the probability of CAD from 48 to 88%. If both test results were negative, the likelihood of CAD was 17%, with only 1 patient (3%) having multivessel CAD. The CKG stress test as a diagnostic device appears most helpful in patients with atypical symptoms and intermediate pretest risk of CAD.

The inter- and intraobserver variability of CKG interpretations was comparable to that reported for thallium scanning without computer assistance.[24–26] Inadequate tracings were obtained in 8% of the group, a figure that is dependent on the experience and patience of the operator. Although technically adequate exercise ECG tracings were obtained in all patients, the ECG response may be uninterpretable in the presence of a left bundle branch block or LV hypertrophy on the resting ECG or in the patient taking digitalis preparations. In these patients, the CKG stress test may be helpful.[13]

Although the results of the present study were based upon a consecutive series of patients, the population was selected for cardiac catheterization and thus had a high prevalence of CAD. Our conclusions might not be ap-

plicable to other symptomatic patients not undergoing catheterization or to asymptomatic subjects whose pretest risk of CAD would be lower.

In summary, the results of the present investigation establish the CKG stress test as a useful noninvasive technique for the detection of CAD. It can be performed in conjunction with the standard exercise electrocardiogram to provide additional diagnostic information as an independent marker for myocardial ischemia.

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Rest and Redistribution Thallium-201 Myocardial Scintigraphy to Predict Improvement in Left Ventricular Function After Coronary Arterial Bypass Grafting

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To examine the value of rest and redistribution thallium-201 imaging in predicting improvement in left ventricular (LV) ejection fraction (EF) after coronary artery bypass grafting (CABG), 26 patients with coronary artery disease (CAD) and abnormal LV function were studied. Nineteen patients had pathologic Q waves preoperatively. Rest and redistribution thallium-201 images and radionuclide ventriculograms were obtained before and after CABG, and the thallium scintigrams were evaluated both quantitatively and qualitatively. The patients were divided according to the preoperative thallium scintigrams into 2 groups: Group I (16 patients) had either normal resting thallium-201 images or reversible resting perfusion defects, and Group II (10 patients) had fixed resting perfusion defects. The resting EF was <50% preoperatively in all patients. Fourteen patients (54%) showed improvement in EF postoperatively. Three patients (2 in Group I and 1 in Group II) showed new postoperative perfusion defects, and none of the 3 showed improvement in LV function. Of the remaining 14 patients in Group I, 12 (86%) showed improvement in LV function, compared with 2 of 9 patients in Group II ($p < 0.01$). Improvement in LV function was observed in 8 of the 19 patients (42%) with abnormal Q waves. Nitroglycerin intervention radionuclide ventriculograms were obtained in 20 patients before CABG. Of the 6 patients who showed improvement in LV function with nitroglycerin, 4 also showed improvement postoperatively. Postoperative improvement in LV function was also observed in 6 of the 14 patients who did not improve with nitroglycerin.

Thus, rest and redistribution thallium imaging is useful in identifying patients whose LV function will improve after CABG. Normal rest thallium-201 images or reversible resting defects correctly identified 12 of 14 patients (86%) who showed improvement in LV function postoperatively. Nitroglycerin-intervention ventriculography and abnormal Q waves were less useful in this differentiation.

Thallium-201 myocardial perfusion imaging has been found to be a useful diagnostic test for coronary artery disease (CAD).[1] The pharmacokinetic features of thallium-201 have been well studied in humans and in nonhumans.[2,3] The delayed or redistribution images reflect the cellular and enzymatic integrity of the myocardium. Normalization of defects present in the postexercise images has been taken as evidence of cellular viability. In this study, we evaluated the potential use of rest and redistribution thallium-201 scintigraphy to predict improvement in global left ventricular (LV) function after coronary artery bypass grafting (CABG).

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Methods

Patients: The patient population consisted of 26 patients: 22 men and 4 women aged 41 to 69 years (mean 59). These patients had severe but stable patterns of angina pectoris and were identified after cardiac catheterization because all had (1) severe CAD defined as ≥70% diameter narrowing of 1 or more major vessels, (2) abnormal LV ejection fraction (EF) by contrast left ventriculography (<50%), and (3) underwent CABG.

These patients were consecutive patients in whom radionuclide angiographic and perfusion studies were available pre- and postoperatively. Because of the severity of symptoms, exercise studies were not performed. Four additional patients were excluded because they died in the perioperative period and thus postoperative studies were not available. All 4 patients had very poor LV function and large fixed perfusion defects consistent with scar.

Patients with preoperative LV EF ≥50% were excluded because improvement in LV function is not expected in these patients after CABG. Also, patients with LV aneurysms that required resection were excluded. No patient had had recent myocardial infarction (within 3 months before the study) and none required concomitant valve replacement (Table I).

TABLE I Pertinent Data in the Study Population

Pt	Age (yr) & Sex	CAD #VD	ECG	Preop Thallium-201 PD Rest	Preop Thallium-201 Improved Delayed	Preop Thallium Score Rest	Preop Thallium Score Delayed	Preop EF (%) Rest	Preop EF (%) NG	Postop Thallium PD	Postop Thallium Score	Postop EF (%)	Postop New ECG Changes	Postop Peak CPK	Postop Peak CPK-MB (%)
							Group I								
1	65M	3	ST-T	0	0	40	40	45	45	0	40	50	0	5X	0
2*	63F	3	ST-T	0	+	36	36	31	—	Ap,Inf,Sep	25	29	AMI	8X	4%
3	62M	3	IMI	0	0	38	38	45	40	0	38	33	RBBB	5X	4%
4	55M	3	NL	0	0	39	39	39	46	0	40	67	0	3X	0
5	61M	2	IMI	0	0	36	36	37	39	0	36	42	0	7X	4%
6	49M	3	ST-T	0	0	40	40	43	—	0	38	58	0	5X	0
7	65F	2	ST-T	AL,Ap,Sep	+	22	28	41	48	Sep	36	58	0	1X	0
8*	58F	3	IMI	AL,AP,Inf,Pos	+	23	25	30	—	—	—	40	0	2X	0
9	54M	3	IMI	Ap,Inf,Pos	+	24	29	34	39	Ap,Inf,Pos	26	30	0	8X	0
10	41M	3	AMI	AL,Ap	+	26	29	43	41	AL,Ap,Pos	26	28	0	6X	5%
11*	54M	3	IMI	Ap,Inf	+	26	30	28	30	0	37	47	0	15X	5%
12	69M	3	AMI	AL,Ap,Sep	+	20	23	21	28	AL,Ap	26	27	LBBB	7X	0
13*	43M	3	IMI	Ap,Inf	+	32	32	41	38	0	40	58	0	5X	0
14*	62M	2	AMI	AL,Ap	+	30	30	42	—	0	38	49	0	3X	0
15*	69F	3	ST-T	Ap,Inf,Pos	+	31	33	32	—	Inf	34	47	0	3X	0
16	52M	3	AMI	AL,Ap,Sep	+	20	28	27	28	Ap,Sep	28	32	0	5X	0
							Group II								
17	63M	2	IMI	Ap,Inf	0	22	22	43	40	Ap,Inf	26	54	0	2X	0
18	63M	2	ST-T	Sep,Ap	0	28	29	33	43	Sep,Ap	29	52	0	11X	2%
19	59M	1	AMI	AL,Ap,Sep	0	20	20	22	26	AL,Ap,Sep	21	23	0	1X	0
20	59M	2	IMI	Ap,Inf,Pos	0	28	29	30	—	Ap,Inf,Pos	29	31	0	2X	0
21	54M	3	AMI,IMI	Sep,Ap	0	34	34	30	36	0	38	30	0	9X	0
22	60M	3	IMI	Ap,Inf,Sep	0	28	28	31	30	Ap,Inf,Pos	27	27	IVCD	14X	4%
23	63M	3	AMI,IMI	AL,Ap	0	31	31	37	37	AL,Ap	29	37	0	7X	0
24	52M	3	AMI	AL,Ap	0	22	23	25	27	AL,Ap	22	26	0	2X	0
25	57M	3	AMI,IMI	Sep,Ap,Inf,Pos	0	22	22	14	15	Sep,Inf,Ap,Pos	22	16	0	3X	0
26	68M	2	IMI	Inf,Pos	0	33	33	24	25	Ap,Inf,Pos	25	20	0	8X	2%

The highest levels of enzymes during the first 3 postoperative days are shown. X is the upper limit of normal in our laboratory for creatine phosphokinase. * = abnormal washout by circumferential radial activity analysis; — = not done.

AL = anterolateral; AMI = anterior myocardial infarction; Ap = apex; CAD = coronary artery disease; CPK = creatine phosphokinase; ECG = electrocardiographic; EF = ejection fraction; Inf = inferior; IMI = inferior myocardial infarction; IVCD = intraventricular conduction delay; CPK-MB = isoenzyme of creatine phosphokinase; LBBB = left bundle branch block; NG = nitroglycerin; NL = normal; #VD = number of vessel disease; PD = perfusion defect; Pos = posterior; Postop = postoperative; Preop = preoperative; Pt = patient; RBBB = right bundle branch block; Sep = septum; ST-T = ST segment and T-wave abnormalities.

CABG was performed utilizing the autogenous reversed saphenous vein in each patient with use of moderate systemic hypothermia and potassium cardioplegia. One to 3 days before the operation, each patient underwent thallium-201 imaging and radionuclide ventriculography. These studies were repeated 7 to 10 days postoperatively.

Radionuclide ventriculograms were obtained using the first-pass method with a multicrystal gamma camera (Baird-Atomic System-77).[4] Radionuclide ventriculography was repeated in 20 patients after sublingual administration of nitroglycerin, administered until there was ≥10% decrease in systolic blood pressure or a 10% increase in heart rate.

Thallium-201 myocardial scintigraphy: Myocardial scintigrams were obtained at rest in all patients after an overnight fast following intravenous injection of 2 mCi of thallium-201. Delayed (or redistribution) images were repeated after 4 hours in the same projections. In 11 patients, the pre- and postoperative images were obtained with the multicrystal camera. The technique for imaging and processing has been described in detail elsewhere.[5,6] In the remaining 15 patients, pre- and postoperative images were obtained with an Ohio Nuclear Series 420 mobile scintillation camera equipped with a low-energy, all-purpose, parallel-hole collimator. The images were subjected to 9-point weighted smoothing and interpolative background subtraction by the method described in detail elsewhere.[7] Circumferential profiles were obtained from the rest and redistribution images. A computer-generated circumference was constructed around the outer edge of the left ventricle, and radii were then constructed by the computer from the image-center to each point on the circumference, each radius being separated from the others by 6°. The average activity per pixel along the radius was calculated. A curve representing the normalized thallium activity versus the angular location was described starting from the radius, oriented at 3 o'clock, and proceeding counterclockwise. The rest and redistribution curves were aligned and displayed together.[7]

Redistribution was considered to have occurred when there was "filling in" of the defects, which in most cases was due to slower washout from the abnormal segment compared with the normal segment. Less commonly, the activity profile showed another pattern characterized by higher activity in the redistribution image compared with the same segment in the initial images. The abnormal washout was often associated with visually apparent filling in of the perfusion defects that were present in the initial images. Occasionally, however, this pattern of abnormal washout was seen in a segment that subjectively was interpreted as normal.

Finally, the images in the anterior and the left anterior oblique projections from both the rest and the redistribution studies were each divided into 5 segments. The activity in each segment was graded as follows: 4+, normal; 3+, mildly decreased; 2+, moderately (but definitely) decreased; 1+, severely decreased; or 0, absent.

The thallium images were interpreted randomly by 2 observers without knowledge of which scans were preoperative and which were postoperative and without knowledge of other test results. There were no major disagreements between the

2 observers related to the presence or absence of perfusion defects. Minor disagreements related to the scoring of the defects or to the extent of the defects were resolved by discussion.

Electrocardiograms and isoenzyme studies were obtained for at least the first 3 days after the operation to determine the presence or absence of perioperative infarction. Seven to 10 days after the operation a rest radionuclide ventriculogram and rest thallium-201 scintigram were obtained as described. Because the radionuclide ventriculograms were obtained in 1 projection (anterior), which enables evaluation of wall motion in only 3 segments, evaluation of wall motion is not discussed in this study.

Postoperative improvement in LV function was defined as ≥5% increase in EF compared with the control measurement obtained preoperatively.

Statistical analysis: Statistical analysis was performed with the *t* test and the chi-square test. A p value <0.05 was considered statistically significant.

Results

One patient had 1-vessel disease, 6 patients had 2-vessel disease, and 19 patients had 3-vessel disease (Table I). The resting electrocardiograms showed previous transmural infarction in 19 patients. The cardiac enzymes did not appear useful in the diagnosis of perioperative infarction. There was no significant change in end-diastolic volume (measured by radionuclide angiography) after CABG (246 ± 73 ml preoperatively versus 236 ± 72 ml postoperatively; difference not significant). Similarly, there was no significant change in the systolic blood pressure; however, the heart rate was significantly higher after CABG (66 ± 9 beats/min preoperatively versus 85 ± 12 beats/min postoperatively; $p<0.001$), probably because many patients were not receiving propranolol after CABG.

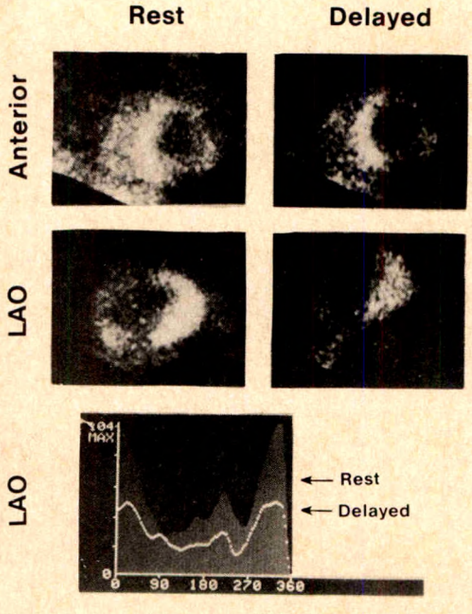

FIGURE 1. Rest and delayed thallium-201 images in a patient with 3-vessel disease. The scans are abnormal, showing fixed defects. The circumferential profile analysis in the initial and delayed images in the left anterior oblique (LAO) projection is also shown.

Thallium-201 myocardial scintigrams: Resting perfusion defects were present in 20 of the 26 patients (77%) (Table I). Qualitative analysis showed reversible defects in 6 patients and fixed defects in 14 patients. An abnormal washout was present in 4 of the 14 patients with fixed defects. The abnormal washout was detected in segments with apparently normal perfusion patterns. All such areas were, however, subserved by severely stenotic coronary vessels. The remaining 10 patients had only fixed defects (Fig. 1). Furthermore, 1 of the 6 patients with normal resting scans had an abnormal washout, indicating the presence of global hypoperfusion. Therefore, a total of 11 (42%) of the 26 patients had redistribution in the delayed images.

Comparison of pre- and postoperative studies: The patients were divided into 2 groups. Group I patients had either normal resting scans or reversible perfusion defects (16 patients); Group II patients (10) had fixed defects only (Table I, Fig. 3 and 4).

Four of the 6 patients with normal scans had improvement in EF after CABG. A new perfusion defect was detected postoperatively in 1 of the 2 patients who did not show such improvement (Patient 2; Table I, Fig. 3 to 5).

In 8 of 10 patients with reversible perfusion defects, there was improvement in the thallium images (Fig. 2 and 4) and improvement in LV EF after CABG (Fig. 3 and 5). The remaining 2 patients (9 and 10, Table I) showed no improvement in LV EF and 1 of the 2 patients showed new perfusion defects postoperatively (Patient 10).

In Group II, 7 of 10 patients had no change in EF postoperatively. Two patients had improvement in EF but no change in thallium images (Patients 17 and 18; Table I, Fig. 3 to 5). One patient had a lower thallium score and a new perfusion defect postoperatively (Patient 26, Table I). Most patients who showed improvement in thallium scans in the delayed and postoperative studies had initial thallium scores between 20 and 26.

If the 3 patients with the new appearance of defects are excluded, then 12 of the 14 patients (86%) in Group I had improvement in EF after CABG, compared with 2 of 9 patients in Group II ($p<0.01$).

Thus, 14 of the 26 patients (54%) showed improvement in global LV EF postoperatively (Fig. 5), and the

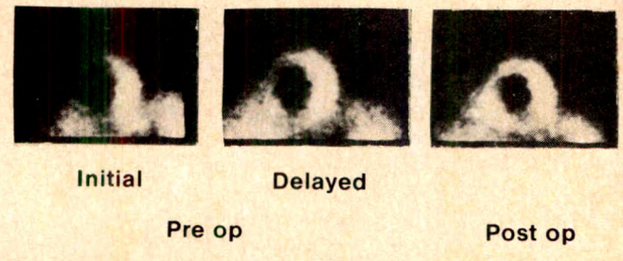

FIGURE 2. Rest thallium-201 images in the 30° left anterior oblique projection before and after coronary artery bypass surgery. The preoperative (Preop) image shows a large defect involving the septum and inferoapical segment. The postoperative (Postop) image shows improvement of perfusion. The delayed preoperative study showed partial redistribution.

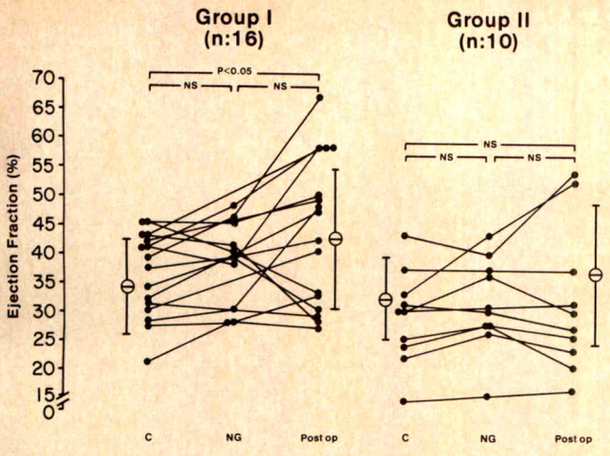

FIGURE 3. Left ventricular ejection fraction in the control state (C), after nitroglycerin (NG), and after operation (Postop). Means ± standard deviation are also shown. n = number of patients; NS = not significant.

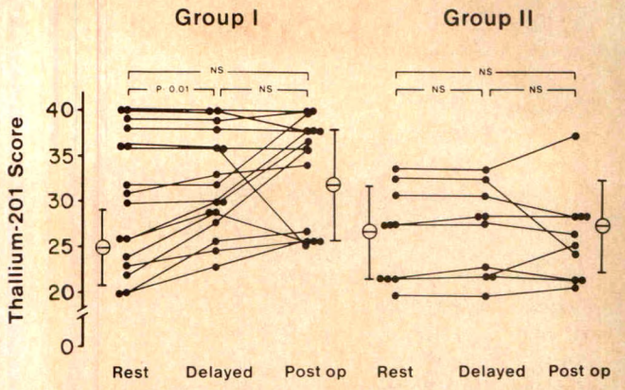

FIGURE 4. Total thallium scores before (rest and delayed) and after surgery (Postop). Means ± standard deviations are also shown. NS = not significant.

change in EF was correctly predicted in 83% of the patients. Eight (42%) of the 19 patients with previous transmural infarction showed improvement in LV EF postoperatively.

Nitroglycerin-intervention ventriculograms: In 20 patients for whom nitroglycerin-intervention radionuclide ventriculograms were available, 6 showed improvement in EF with nitroglycerin (≥5% increase in EF). The rather low percentage of improvement with nitroglycerin is probably because many patients had prior infarction. Of those, 4 showed improvement in EF after CABG. On the other hand, of the remaining 14 patients who showed no improvement in EF with nitroglycerin, 6 patients (43%) had improvement in the EF postoperatively. Thus, nitroglycerin radionuclide ventriculograms predicted the correct change in only 12 of the 20 patients (60%) (Fig. 5).

The predictive value of thallium scintigraphy (83%) was higher than that of nitroglycerin radionuclide ventriculograms (60%), or that of the abnormal Q waves (42%).

Discussion

In this study, we found areas with transient resting hypoperfusion by means of rest thallium-201 images in 11 of the 26 patients (42%). The reversible perfusion abnormalities were seen in the absence of clinically evident episodes of myocardial ischemia. This finding is consistent with those in other reports.[8,9]

Changes in LV function after CABG have been extensively studied, but the results have been conflicting.[10–23] The reasons for these disparate results may be traced to several factors: First, patients with normal LV function preoperatively are unlikely to have improvement in function postoperatively. Second, the presence of perioperative infarction may cause deterioration in LV function postoperatively. However, early investigators did not utilize technetium-99m pyrophosphate studies, which have been shown to increase reliability in detecting perioperative infarction.[24–27] Depression of LV function may also be due to myocardial ischemia and injury during cardioplegic arrest.[28] Third, improvement in segmental asynergy may occur with no obvious change in global LV function.[29]

In this study, we found that patients with abnormal LV function may have a normal resting perfusion pattern, reversible defects, or fixed defects, suggesting different causes for LV dysfunction. LV global function improved after surgery in 14 (54%) of the 26 patients; the improvement was more likely to occur in patients with normal scans and or reversible defects than in those with fixed defects ($p < 0.01$).

The occurrence of perioperative infarction, graft occlusion, or intraoperative ischemia may have contrib-

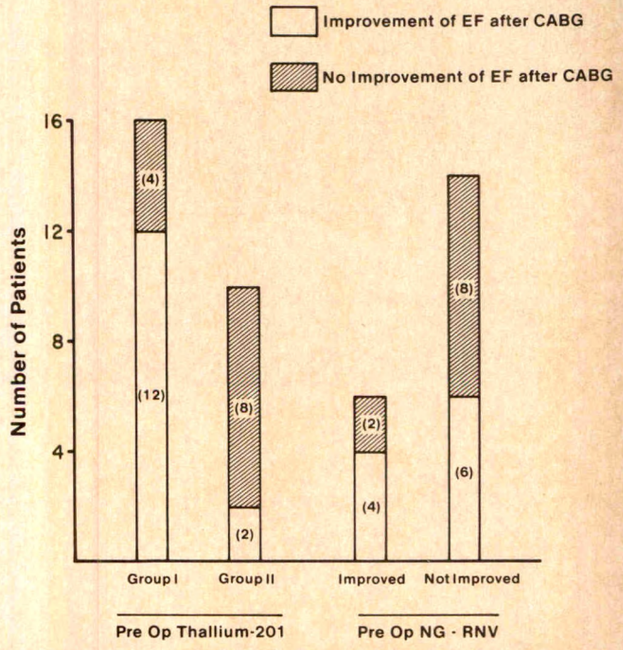

FIGURE 5. Changes in left ventricular ejection fraction (EF) after coronary artery bypass grafting (CABG) in relation to the results of preoperative (Preop) thallium-201 images and nitroglycerin (NG)-intervention radionuclide ventriculograms (RNV). Group I patients had normal scans or transient defects; Group II patients had fixed defects.

uted to the absence of improvement in EF in 2 patients (1 with reversible defect and 1 with normal scans). Similarly, it is not clear why the 2 patients with fixed defects showed improvement in LV function postoperatively. The changes in preload and afterload postoperatively in the second patient who had no change in thallium score may have contributed to the improvement. It appears, therefore, that rest and redistribution thallium imaging predicted the correct change in postoperative LV function in 83% of the patients, whereas the predictive accuracy of nitroglycerin-intervention radionuclide ventriculography was 60%. Finally, abnormal Q waves did not preclude improvement in LV function.

Clinical implications: Patients with abnormal LV function constitute a heterogeneous population that can be separated into such groups on the basis of the resting perfusion pattern. This study may provide guidelines for recommending bypass surgery in patients with coronary artery disease and minimal or no symptoms if improvement in LV function is the main indication for surgery. It should be emphasized that our results are related to resting LV function. Improvement in exercise LV function has been reported in most patients after coronary artery bypass surgery.[30]

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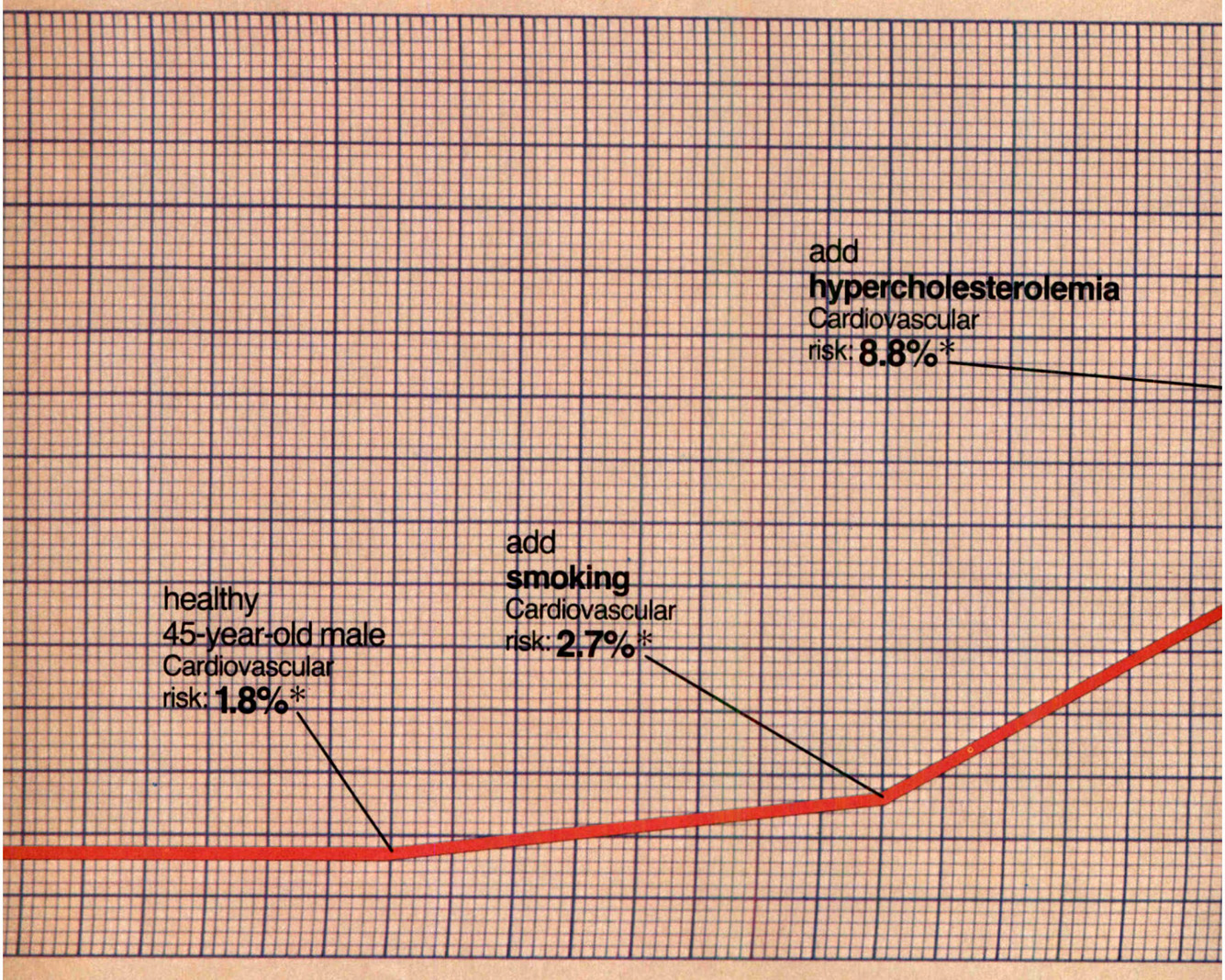

Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

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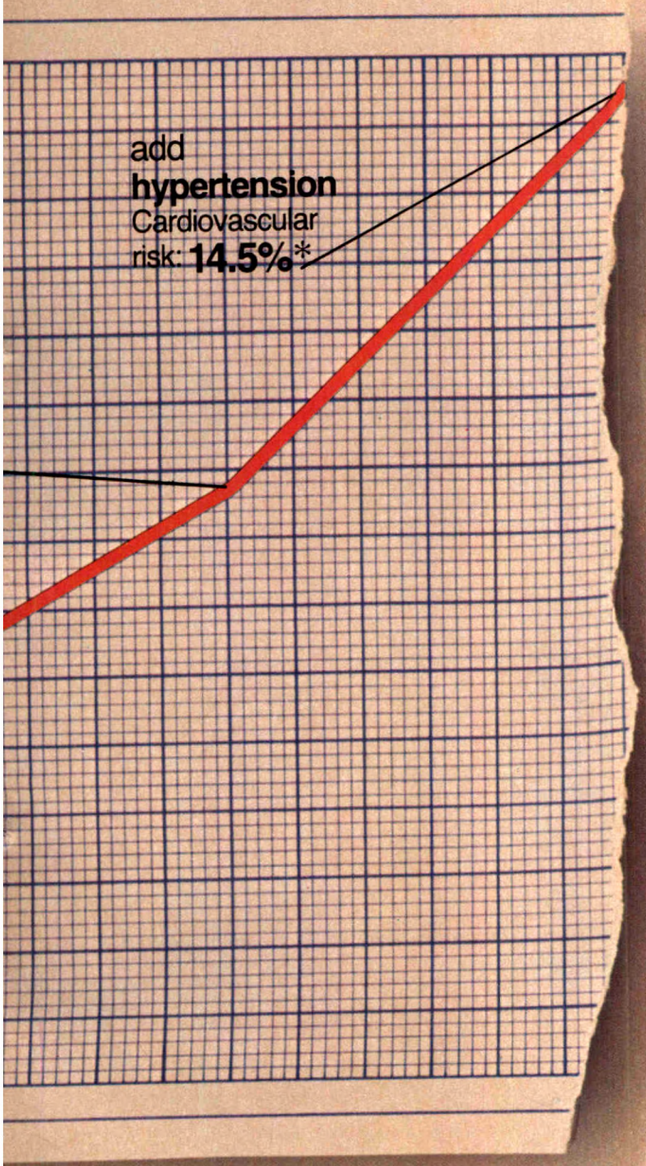

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Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

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Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

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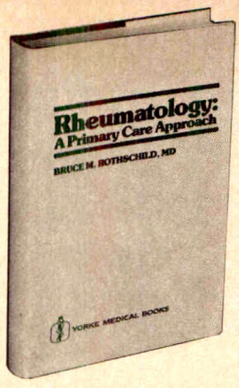

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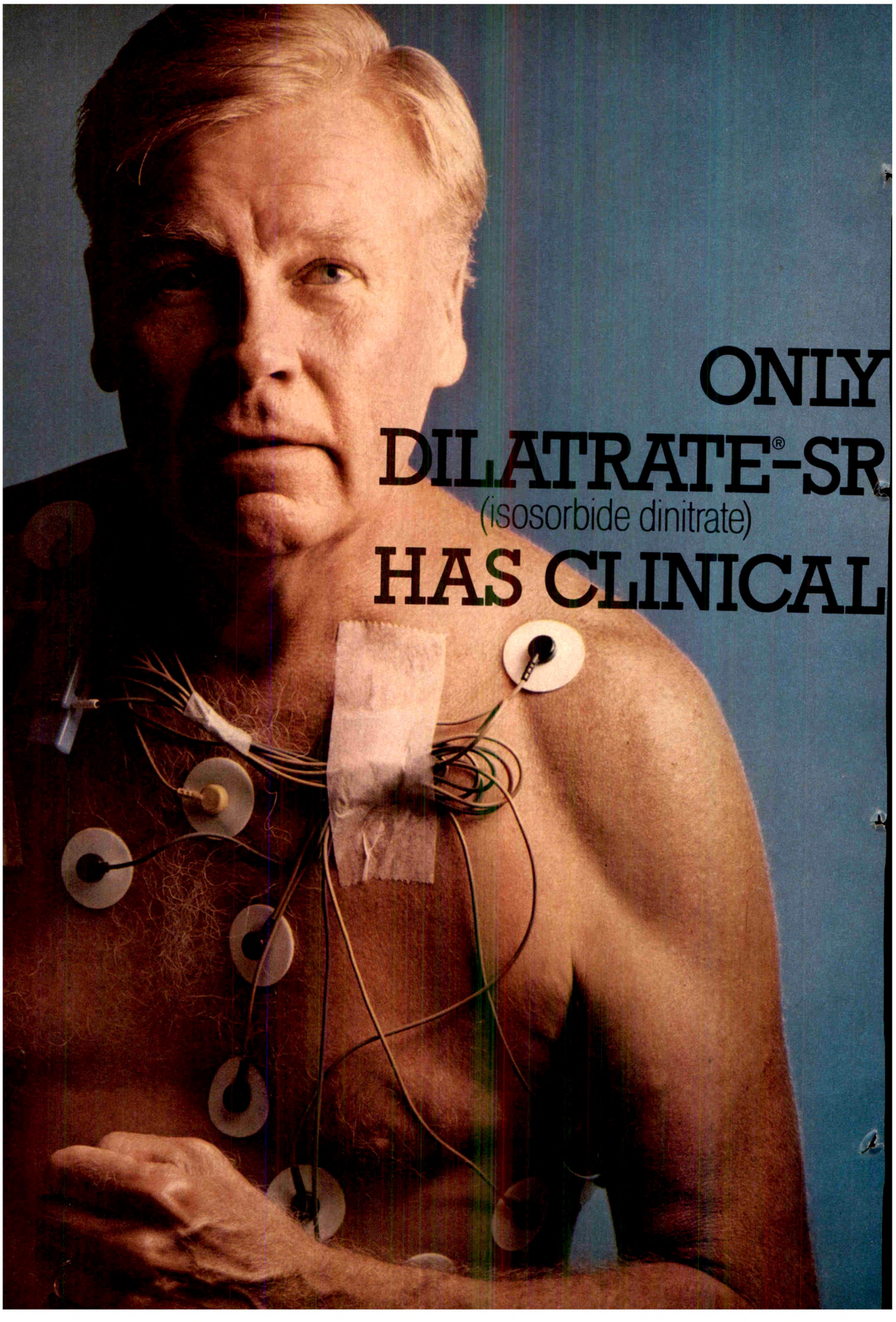
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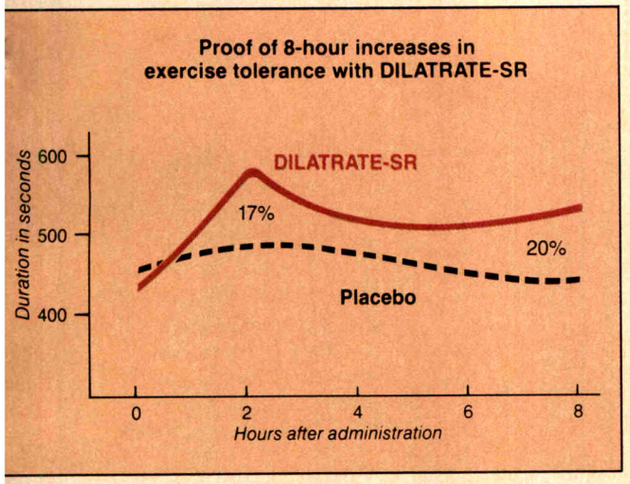

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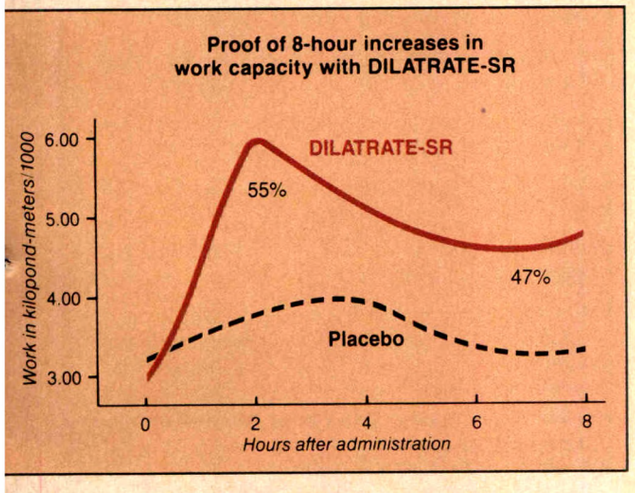

20% increase in duration of treadmill exercise means nother minute or two at higher speed on a steeper ncline. When mean work performance was calculated,)ILATRATE-SR provided a 47% increase at 8 hours.

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The proven sustained activity of DILATRATE-SR offers anginal patients convenient b.i.d. dosage and can reduce the need for sublingual nitroglycerin.

*Please see brief summary of full prescribing information on following page. For full prescribing information, consult package insert.

References:

1. DiBianco R et al: Effects of a new oral slow release form of isosorbide dinitrate on the hemodynamics and exercise capacity of patients with angina — a placebo controlled and double blind study. *Circulation* (Supp II) 66:381, Oct 1982.
2. Dinsdale J, Allen J: Data on file, Medical Department, Reed & Carnrick.

Dilatrate®-SR
(isosorbide dinitrate) 40 mg

Reed & Carnrick / Piscataway, New Jersey 08854

Dilatrate®-SR
(isosorbide dinitrate) 40 mg

BRIEF SUMMARY

Indications: Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: When taken by the oral route, is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATION: Idiosyncrasy to this drug.

WARNINGS: Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS: Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

ADVERSE REACTIONS: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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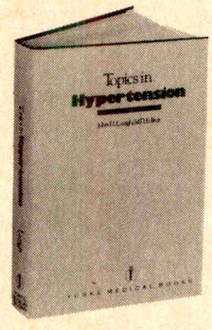
Laragh's eagerly awaited new book on the silent killer

TOPICS IN HYPERTENSION



Edited by
John H. Laragh, MD
Master Professor of Medicine
Director, The Cardiovascular Center Chief, Cardiology Division The New York Hospital-Cornell Medical Center

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Each packet (2.8 g) provides 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, and L-lysine monohydrochloride 0.913 g.

The patient on higher doses of antihypertensive medication, diuretics and/or digitalis, may need additional potassium supplementation...40 mEq/day or more. KLORVESS Effervescent Granules offer the following advantages:

- ***Each packet delivers 20 mEq of potassium***...compared with slow-release tablets that contain 10 mEq or less.
- ***Sparkling citrus flavor offers a high degree of patient compliance.*** Patients may even use KLORVESS as a "chaser" for other medications. Granules mix easily with cold water...no need for expensive juices to make palatable.
- ***Convenient effervescent granules dissolve almost immediately***...no waiting.
- ***Sugar-free, sodium-free, carbohydrate-free, dye-free formulation***...ideal for hypertensive, diabetic, or overweight patients.

PHARMACEUTICAL DIVISION
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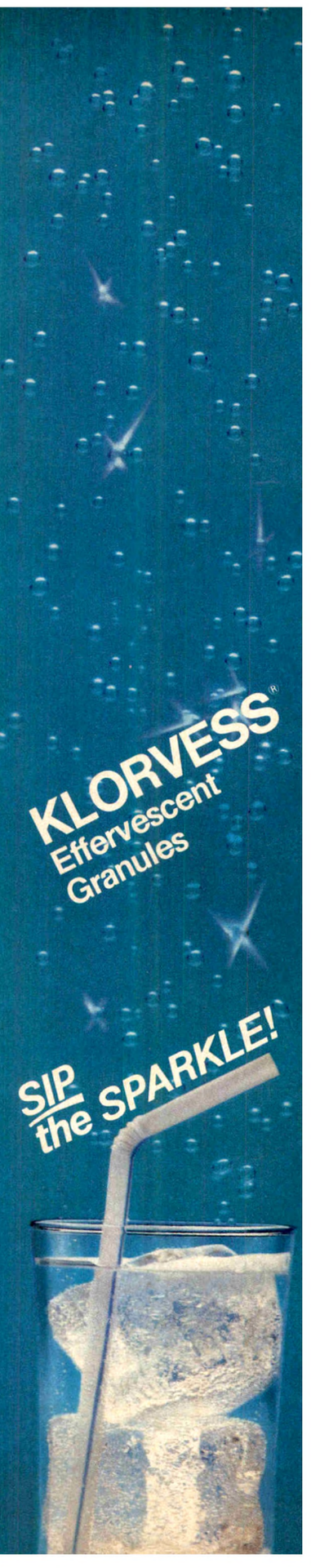
Please see brief summary of prescribing information on adjoining page.

KLR-582-1



Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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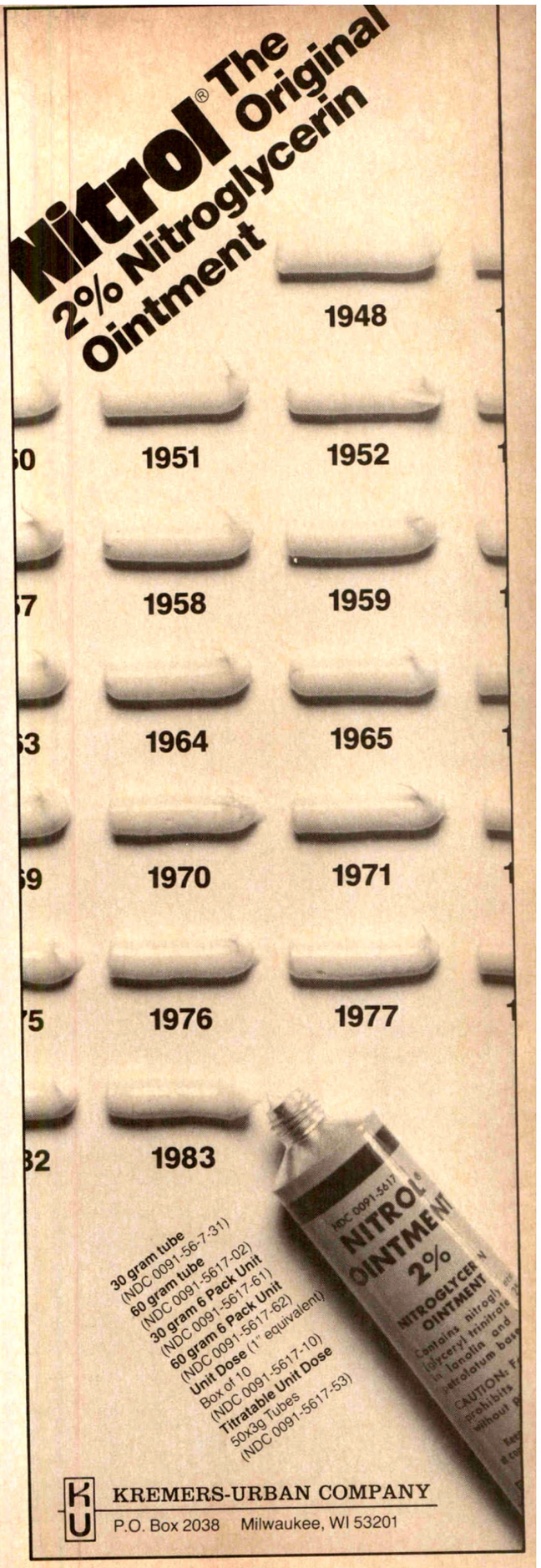

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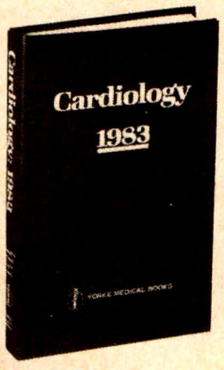

Cardiology 1983

Written by
William C. Roberts, MD
Dean T. Mason, MD
Thomas P. Graham, MD
Robert B. Karp, MD
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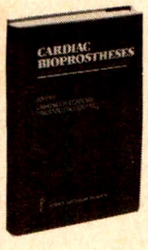
ISBN 0-914316-36-2, approx. 500pp., illus., June '83, approx. $45.00



Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by,
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Foreword by David H. Spodick, MD

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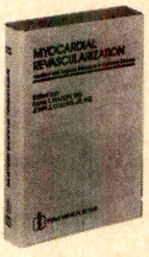
ISBN 0-914316-35-4, 200pp., illus., large format 8¾×12, March '83, $65.00



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ISBN 0-914316-37-0, approx. 350pp., illus., Fall '83, approx. $35.00

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ISBN 0-89335-096-6
496pp., illus., large format 8½×11, 1983, $80.00

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Your Right to Know... The Facts in Black and White

FACT: Calan® (verapamil HCl) is the calcium antagonist consistently demonstrating antianginal benefits equal to, or greater than, propranolol, at clinically used doses in angina of effort.[1,2,3,4,5,6]

- Calan is also effective in variant angina[7] (where spasm may be exacerbated by propranolol[8]) as well as in unstable angina.[9]

FACT: In direct-comparative studies, the antianginal benefits of Calan were reported to be unsurpassed by nifedipine.[10,11,12]

- In stable effort angina: "The trial demonstrated a clear difference in the antianginal efficacy of [verapamil (Calan) and nifedipine]. ...Verapamil [Calan] was more effective..."[10] In another study, the efficacy differences were not statistically significant.[11] The doses used in both studies were Calan 120 mg tid and nifedipine 20 mg tid.

  In variant angina, in the one published comparative study, Calan and nifedipine showed equal efficacy. However, this study was neither blinded nor randomized.[12]

- Studies were directly comparative, and responses to each drug were measured objectively.[10,11,12]

FACT: Calan is indicated as single-agent initial therapy for all types of angina, while nifedipine is not.[13,14]

- Nifedipine is indicated in stable effort angina only in patients refractory to or intolerant of nitrates and/or beta-blockers.[14]
- Nifedipine is indicated for unstable angina only when ECG findings indicate vasospasm or the disease is refractory to nitrates and/or beta-blockers.[14]

FACT: The potential serious cardiovascular side effects of Calan are similar to those of beta-blockers.

- Calan and propranolol have basically the same cardiovascular cautions and contraindications such as in patients with ventricular dysfunction, second- or third-degree AV block, or cardiogenic shock.[13,15] Calan is also contraindicated in the presence of sick sinus syndrome or hypotension.
- Calan rarely causes extreme fatigue or mental depression.
- Impotence, memory loss, or nightmares have not been associated with Calan use. Calan may cause constipation.
- Calan can be used without special caution in patients with angina who also have asthma, chronic obstructive pulmonary disease, diabetes mellitus, or peripheral vascular disease such as Raynaud's phenomenon.

FACT: The incidence of adverse effects of Calan and nifedipine merits comparison (see chart below).

Adverse Reactions Reported	nifedipine — Uncontrolled U.S. experience in 2,100 patients. The incidence of adverse reactions in controlled studies was generally the same or higher.[14]	(Calan) verapamil — Clinical studies in 1,166 patients — NOTE that similar results were seen in both controlled clinical trials and uncontrolled clinical experience.[13]
Dizziness, light-headedness	About 10%	3.6%
Constipation	2% or less	6.3%
Flushing	About 10%	*
Headache	About 10%	1.8%
Weakness	About 10%	*
Fatigue	*	1.1%
Nausea	About 10%	1.6%
CHF or pulmonary edema	**	0.9%
Peripheral edema	About 10%	1.7%
AV block: third-degree	*	0.8%
Transient hypotension	About 5%	2.9%
Palpitation	About 2%	*
Bradycardia: HR<50/min	*	1.1%
Syncope	About 0.5%	<0.5%

*Not reported in the prescribing information.[13,14]

**About 2%, "not readily distinguishable from the natural history of the disease." "It remains possible, however, that some or many of these events were drug related."[14]

Calan® (verapamil HCl) **TABLETS** 80 mg and 120 mg

Effective Angina Therapy

Please see reverse side for a brief summary of the complete prescribing information.

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The Facts of Effective Angina Therapy

FACT: Calan® (verapamil HCl) has pharmacologic effects complementary to those of nitrates.[13]

- Like propranolol, Calan decreases myocardial contractility. Calan's effect on the SA node tends to minimize heart rate response to arterial vasodilation, leaving the rate unchanged or slightly reduced.[13]
- Nifedipine tends to cause slightly increased heart rate due to a sympathetic response to arterial dilation.[14]

FACT: Calan provides truly additive effects with propranolol when such combination therapy is necessary in the treatment of chronic stable angina.[3,4]

- In two studies involving a total of 33 patients, the additive effects of Calan with propranolol on exercise tolerance could be seen.

	Study A[3]	Study B[4]
Propranolol alone	+2 min *	+1.3 min
Calan alone	+3.2 min	+3.4 min
Calan with propranolol	+5.3 min	+4.7 min

*Difference from placebo to maximally tolerated exercise

- Combined therapy should be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Because of the still limited experience with combination therapy, Calan should be used alone, if possible.

FACT: Safety considerations are important with Calan, beta-blockers, and nifedipine.

- In patients with normal conduction, Calan's electrophysiologic effects are rarely clinically important.[13] However, Calan's contraindications include patients with sick sinus syndrome or second- or third-degree AV block.
- The concomitant use of digitalis with Calan or nifedipine requires caution because digoxin serum levels may increase.[16,17]
- Both Calan and nifedipine, as well as propranolol and nitrates, require monitoring during upward dose titration.[13,14,15]

For Your Patients With Angina...

Calan® TABLETS 80 mg and 120 mg
(verapamil HCl)

- Calan is the calcium antagonist with consistently demonstrated antianginal benefits equal to or greater than propranolol.
- Calan is effective in variant angina where spasm may be exacerbated by propranolol.[8]
- Calan, unlike nifedipine, has a first-line indication for stable effort angina.

FACT: All the above statements are supported by published materials.

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Calan® (verapamil HCl) TABLETS 80 mg and 120 mg

Contraindications: Severe left ventricular dysfunction (see *Warnings),* hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Occasional elevations of liver enzymes have been reported; patients receiving verapamil should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil. **Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefuly monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR< 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** Calan (verapamil HCl) is supplied in 80-mg and 120-mg sugar-coated tablets.

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Long-Term Converting-Enzyme Inhibition As a Guide to Surgical Curability of Hypertension Associated With Renovascular Disease

JAN STAESSEN, MD, CHRISTOPHER BULPITT, MD, ROBERT FAGARD, MD, PAUL LIJNEN, PhD, and ANTOON AMERY, MD

Converting-enzyme inhibition as a guide to the hypotensive response to be expected from surgery was evaluated in 27 hypertensive patients with renovascular disease. Blood pressure averaged 163 ± 5/102 ± 2 mm Hg (mean ± standard error of the mean) during converting-enzyme inhibition with captopril, 518 ± 29 mg daily for 2.8 ± 0.3 months, and stabilized at a similar level of 165 ± 4/104 ± 3 mm Hg during 5.0 ± 0.6 months of postoperative follow-up, when no medication was administered.

Postoperative pressure, both systolic ($r = +0.53$; $p = 0.004$) and diastolic ($r = +0.55$; $p = 0.003$), was correlated with blood pressure during converting-enzyme inhibition. In addition, multiple regression analysis identified systolic pressure during converting-enzyme inhibition as the only significant ($p < 0.01$) predictor of postoperative systolic pressure. Diastolic pressure during converting-enzyme inhibition ($p < 0.05$) in conjunction with circulating renin ($p < 0.05$) and renin suppression from the contralateral kidney ($p < 0.01$) explained up to 53% of the postoperative diastolic pressure. Therefore, blood pressure during long-term converting-enzyme inhibition may be useful as a predictor of the postoperative blood pressure in hypertensive patients with renovascular disease.

Pharmacologic inhibition of the renin-angiotensin system has been proposed as a means of detecting angiotensin II dependence and hence surgical curability of hypertension in human renovascular disease. Bühler et al[1] reported that the hypotensive response to propranolol and to successful surgery was generally of the same magnitude in patients with renovascular or unilateral renal parenchymal disease. More recently, saralasin testing has been employed in the recognition of "angiotensinogenic" renovascular hypertension, but both false-positive and false-negative results have been reported.[2–4] Furthermore, short-term administration of inhibitors of the renin-angiotensin system is likely to be an unreliable guide to surgical prognosis.[5] Therefore, the present study investigates whether long-term converting-enzyme inhibition with captopril could be useful in predicting the postoperative blood pressure in hypertensive patients with renovascular disease.

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Methods

Patients: After informed consent was obtained, 27 hypertensive patients, 21 men and 6 women, were given captopril and later operated on. These patients, aged 47 ± 3 years (mean ± standard error of the mean) and weighing 73 ± 3 kg, were selected after renal angiography demonstrated an arterial diameter reduction of ≥50%. However, blood pressure response to converting-enzyme inhibition was never employed as an index as to whether or not surgical treatment should be proposed. Renal artery stenoses were caused by atheromatosis (n = 20), fibromuscular hyperplasia (n = 4), or trauma (n = 1), whereas in the remaining 2 patients contrast studies revealed at 1 side a hypoplastic renal artery. Using the World Health Organization criteria (1978), hypertensive cardiovascular disease had progressed to stage 2 in 10 patients and to stage 3 in 13 patients. The serum creatinine level averaged 1.4 mg/dl, ranging from 0.6 to 3.1 mg/dl.

Diagnostic procedures: Before the study renal angiography was performed and obstructive lesions were graded by an independent observer. On a separate day, after overnight

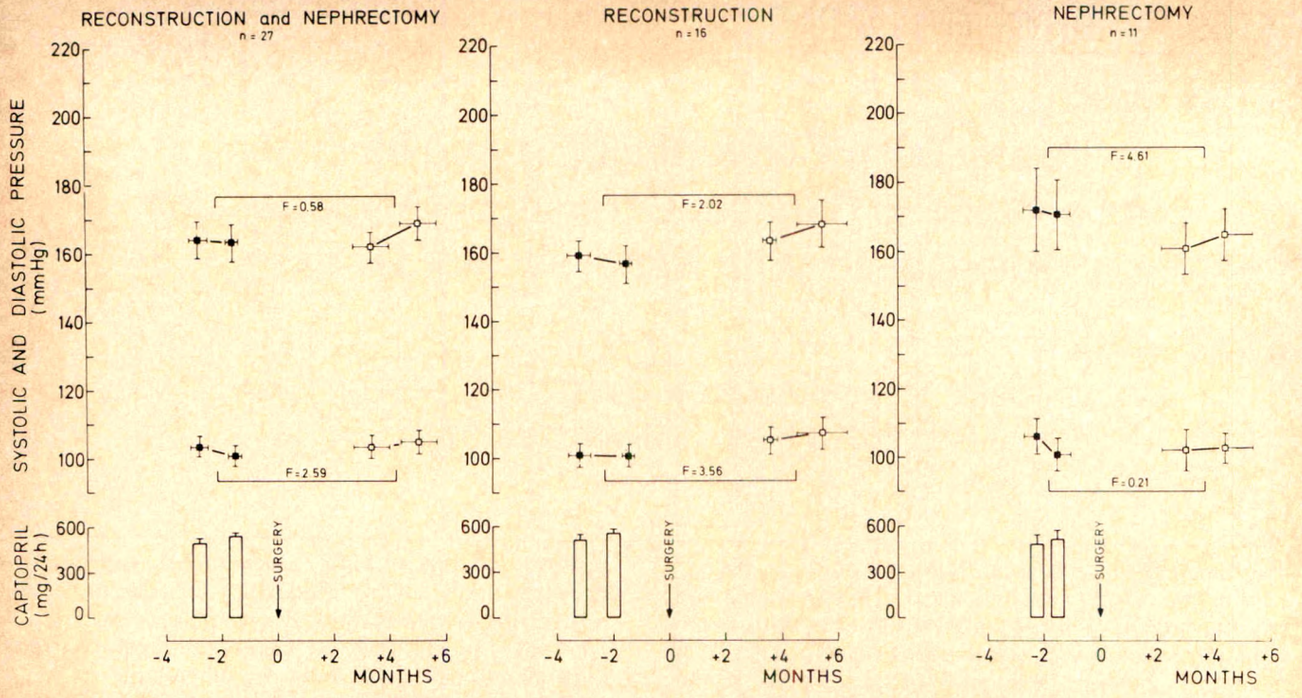

FIGURE 1. Systolic and diastolic blood pressure (mean ± standard error) during converting-enzyme inhibition (**closed symbols**) and postoperative follow-up study (**open symbols**) are given for the total study population (n = 27) and for patients subjected to renal revascularization (n = 16) and nephrectomy (n = 11), separately. The daily dose of captopril is indicated in the lower part of the illustration.

recumbency, blood samples were selectively obtained from the right and left renal vein together with an arterial blood sample. At least 2 consecutive days before the latter procedure, renin secretion had been stimulated by dietary sodium restriction to 50 mEq/24 h and by the administration of a diuretic agent, in most instances chlorthalidone 50 mg/day. Other hypotensive drugs were withheld at least 1 week before renal vein catheterization. When bilateral arterial lesions were present (7 patients), the ipsilateral side was identified as the side with the higher grade stenosis which in all these patients also showed the higher renal vein renin activity.

Study protocol: At the start of the study 18 patients were not receiving antihypertensive medication, whereas in 9 patients medical therapy had been continued for ethical reasons. After entering the study patients were started on (n = 18) or switched to (n = 9) monotherapy with captopril in 3 divided daily doses. The dose of the converting-enzyme inhibitor was doubled every 2 weeks until normotension was achieved or until side effects occurred. A ceiling daily dose of 600 mg was reached in 21 patients: 2 patients were finally prescribed a maximal daily dose of 450 mg and 3 other patients 300 mg, whereas 1 patient became normotensive while taking only 25 mg daily. Captopril treatment was continued on average for 2.8 ± 0.3 months (range 3 to 29 weeks). Thereafter patients came to surgery. Of the 20 patients with unilateral lesions, 12 underwent revascularization and 8 nephrectomy at the diseased site. Of the 7 patients with bilateral renal artery lesions, 2 were subjected to a bilateral bypass operation and 1 to ipsilateral nephrectomy and contralateral revascularization. For further analysis, the latter patient will be classified in the nephrectomy group of patients, because this procedure relieved the functionally significant lesion. Contralateral renal artery lesions were graded <50% in 4 patients who had an ipsilateral to contralateral renal vein renin ratio >2.1. In these 4 patients only the ipsilateral lesion was relieved by either nephrectomy (n = 2) or a bypass operation (n = 2). During the postoperative follow-up averaging 5.0 ± 0.7 months (range 8 to 74 weeks), the patients did not receive hypotensive drug treatment. After renovascular surgery, the patency of the renal artery or its bypass graft was always verified arteriographically.

Patients were examined at regular intervals and always in the early afternoon: results of 1 outpatient visit at the start of the study and of 2 visits during preoperative captopril treatment and postoperative follow-up will be reported. On each visit, blood pressure was measured 5 times consecutively in the supine position. The last 2 pressure readings of each visit were averaged for statistical analysis. The untreated blood pressure available in 18 patients was the pressure recorded in the outpatient clinic after many visits, when the patient had become accustomed to both procedure and visit. Blood was withdrawn from an antecubital vein after the patient had been seated for 15 minutes (during converting-enzyme inhibition approximately 8 hours after the morning dose of captopril). Blood tests included erythrocyte and leukocyte counts and creatinine, blood urea nitrogen, and renin activity determinations,[6] and during captopril treatment and postoperative follow-up also angiotensin I[7] and angiotensin II determinations.[8] Twenty-four–hour urine samples were analyzed for sodium, creatinine, aldosterone,[9] and prostaglandin E_2[10] and $F_{2\alpha}$.[10]

Statistical analysis: Statistical methods included Student's t test for paired observations and 3-way analysis of variance on treatments (captopril versus surgery), order of investigations, and subjects. Proportions were compared by McNemar's test. Regression analysis was performed after linearizing the distribution of plasma renin by a logarithmic transformation. Postoperative blood pressure was correlated with various predictors using Pearson's correlation coefficient. To evaluate the independent contributions of these predictors

TABLE I Results of Blood Analyses in Patients Undergoing Vascular Reconstruction or Nephrectomy

	Reconstruction			Nephrectomy		
	n	Captopril Treatment	Postoperative Follow-Up	n	Captopril Treatment	Postoperative Follow-Up
PRA (ng/ml/h)	16	12.7 ± 2.6	1.2 ± 0.2*	10	19.4 ± 3.4	1.3 ± 0.2*
ANG I (pg/ml)	15	988 ± 238	55 ± 3*	9	1,382 ± 279	80 ± 14*
ANG II (pg/ml)	16	17.1 ± 3.1	16.3 ± 2.5	10	14.3 ± 2.7	14.3 ± 2.4
BUN (mg/dl)	16	20.7 ± 2.7	16.5 ± 1.3†	11	21.0 ± 2.3	17.5 ± 1.4‡
Creatinine (mg/dl)	16	1.40 ± 0.10	1.08 ± 0.06*	11	1.52 ± 0.15	1.45 ± 0.13‡

Significance of the difference between preoperative captopril treatment and postoperative follow-up: * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$.
ANG I and ANG II = plasma angiotensin I and II concentration; BUN = blood urea nitrogen; n = number of patients included in the analysis; PRA = plasma renin activity.

TABLE II Results of Urine Analyses in Patients Undergoing Vascular Reconstruction or Nephrectomy

	Reconstruction			Nephrectomy		
	n	Captopril Treatment	Postoperative Follow-Up	n	Captopril Treatment	Postoperative Follow-Up
UAE (μg/24 h)	11	5.7 ± 1.4	7.2 ± 1.1	8	10.2 ± 4.5	9.6 ± 3.5
$UPGE_2$ (ng/24 h)	8	741 ± 331	781 ± 486	5	320 ± 117	239 ± 63
$UPGF_{2\alpha}$ (ng/24 h)	8	952 ± 221	834 ± 128	6	983 ± 100	637 ± 92*
Cr Cl (ml/min)	16	94 ± 11	102 ± 10	11	79 ± 12	87 ± 12

Significance of the difference between treatment and postoperative follow-up: * $p < 0.01$.
n = number of patients included in the analysis; Cr Cl = creatinine clearance; UAE, $UPGE_2$, and $UPGF_{2\alpha}$ = urinary excretion of aldosterone and prostaglandin E_2 and $F_{2\alpha}$.

to the postoperative pressure, multiple regression equations were calculated by a step-down procedure, terminating when all retained regression coefficients were significant at the 5% level.[11]

Results

Effects of converting-enzyme inhibition and surgery: In the 18 initially untreated patients, arterial pressure decreased ($p < 0.001$) from 194 ± 8/122 ± 4 mm Hg to 154 ± 4/97 ± 3 mm Hg during captopril treatment and stabilized at 161 ± 6/105 ± 4 mm Hg during postoperative follow-up. In these patients captopril produced an increase ($p < 0.001$) in plasma renin activity from 6.6 ± 2.5 to 17.1 ± 2.8 ng/ml/h. Nine patients were still on hypotensive drug treatment at the start of the study, when their blood pressure averaged 189 ± 12/113 ± 6 mm Hg. During captopril intake their pressure was decreased to 182 ± 11/110 ± 4 mm Hg and postoperatively to 174 ± 6/103 ± 4 mm Hg, but these effects were statistically not significant.

Comparison between converting-enzyme inhibition and surgery: Analysis of variance showed that independent of the nature of treatment (converting-enzyme inhibition or surgery), none of the variables was influenced by the order of the observations; therefore, average values will be reported for both outpatients during each treatment period.

As shown in Figure 1, blood pressure levels were similar during captopril treatment and postoperative follow-up when all patients (n = 27) were considered together. This also was true when patients subjected to vascular surgery (n = 16) or nephrectomy (n = 11) were analyzed separately.

Results of relevant blood and urine analyses performed during captopril treatment and postoperatively are presented in Tables I and II, separately for patients subjected to reconstructive vascular surgery (n = 16) and nephrectomy (n = 11). In both groups serum creatinine and blood urea nitrogen decreased after surgery compared with results after captopril treatment, whereas the changes in creatinine clearance, although in the same direction, did not reach a level of statistical significance. This could be related to the higher variability of the latter measurement. Plasma renin activity ($p < 0.001$) and angiotensin I ($p < 0.001$) decreased after either operative procedure. In contrast, angiotensin II and aldosterone were similar during converting-enzyme inhibition and after surgery. Compared with its value during converting-enzyme inhibition, the angiotensin I/angiotensin II ratio declined from 59 ± 12 to 5 ± 1 in patients subjected to renal revascularization (n = 15; $p < 0.001$) and from 112 ± 21 to 8 ± 2 in patients with nephrectomy (n = 9; $p < 0.001$), confirming that during captopril administration a smaller proportion of circulating angiotensin I was converted to angiotensin II. Prostaglandin E_2 and $F_{2\alpha}$ were not affected in 8 patients subjected to renal revascularization, whereas prostaglandin $F_{2\alpha}$ decreased ($p < 0.01$) in 6 patients with nephrectomy.

At the start of the study urinary output and urinary sodium excretion averaged 1.8 ± 0.1 liters/24 h and 118 ± 17 mEq/24 h, respectively, and thereafter did not change significantly, suggesting that patients remained on a constant sodium intake. Separate analysis of patients with bilateral renal artery stenosis is presented in Table III. Also in these patients, blood pressure and angiotensin II levels were similar during both treatment periods, whereas renal function improved after surgery.

TABLE III Results in 7 Patients With Bilateral Renal Artery Stenosis

	n	Captopril Treatment	Postoperative Follow-Up
Systolic pressure (mm Hg)	7	166 ± 10	161 ± 7
Diastolic pressure (mm Hg)	7	100 ± 5	99 ± 2
Plasma renin activity (ng/ml/h)	7	19.6 ± 4.1	1.6 ± 0.4*
Plasma angiotensin I (pg/ml)	6	1411 ± 360	68 ± 11*
Plasma angiotensin II (pg/ml)	7	11.6 ± 2.2	12.9 ± 4.0
Urinary aldosterone (μg/24 h)	4	3.7 ± 1.4	6.3 ± 0.8
Blood urea nitrogen (mg/dl)	7	30.4 ± 4.5	18.5 ± 2.0*
Serum creatinine (mg/dl)	7	1.86 ± 0.21	1.39 ± 0.15†
Creatinine clearance (ml/min)	7	71 ± 11	82 ± 5‡

Significance of the difference between preoperative captopril treatment and postoperative follow-up: * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$.
n = number of patients included in the analysis.

Prediction of postoperative blood pressure: Postoperative blood pressure, both systolic and diastolic, correlated positively ($p < 0.01$) with the pressure level during converting-enzyme inhibition (Fig. 2). Also, there was a significant and positive relation between postoperative diastolic pressure and the contralateral renal vein to arterial renin ratio ($r = +0.55$; $p < 0.01$). In the 18 patients in whom measurements of untreated blood pressure were available, it was possible to compare the predictive power of these readings with the prediction based on captopril pressures. For these subjects untreated pressures were correlated with postoperative pressures, yielding correlation coefficients of +0.45 for systolic and +0.44 for diastolic pressure ($p = 0.06$). The corresponding results for the captopril and postoperative pressures were +0.64 ($p = 0.004$) and +0.75 ($p < 0.001$) in these 18 patients. The captopril pressure predicted systolic and diastolic postoperative pressure within ±20 mm Hg in 67 and 78% of these 18 patients, respectively. This was significantly ($p = 0.05$) better than the 28% prediction with untreated systolic pressure, but not significantly better than the 50% prediction with untreated diastolic pressure. In this study it was not investigated whether the blood pressure prediction by another drug would give a worse or better result.

Stepwise multiple regression analysis identified systolic pressure during captopril administration as the only significant predictor of systolic pressure after surgery (postoperative systolic pressure = 0.45 systolic pressure during captopril + 91.9; $r = 0.53$; $p < 0.01$). However, the partial correlation between postoperative systolic pressure and arterial plasma renin activity (measured at the time of renal vein catheterization) just failed to reach statistical significance ($t = -2.01$; $p = 0.056$). For postoperative diastolic pressure the following equation was derived: postoperative diastolic pressure = 0.54 diastolic pressure during captopril − 10.5 $\log_{10}$ arterial plasma renin activity + 19.7 contralateral renal vein to arterial renin ratio + 40.5 ($r = 0.73$; $p < 0.001$). This equation indicates that the hypotensive potential of surgical treatment increased when captopril was more effective in reducing blood

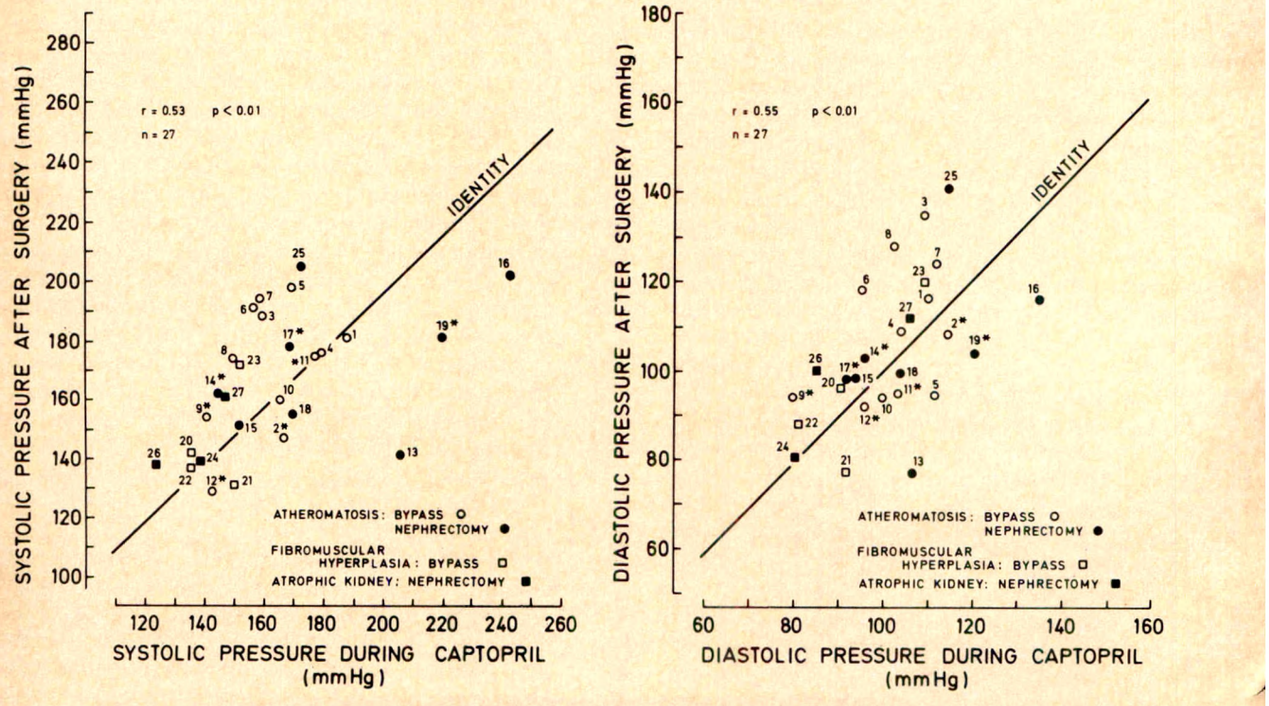

FIGURE 2. Systolic (**left**) and diastolic (**right**) pressure observed after surgery is plotted on the y axis against the pressure levels achieved by converting-enzyme inhibition (captopril) on the x axis. **Symbols** indicate for each patient, identified by the same number of both panels, the underlying condition and the surgical procedure used: **open circles** = atheromatosis and bypass; **closed circles** = atheromatosis and nephrectomy; **open squares** = fibromuscular hyperplasia and bypass; and **closed squares** = renal parenchymal atrophy and nephrectomy. **Asterisks** indicate patients with bilateral renal artery stenoses.

pressure ($p < 0.05$), when the peripheral (arterial) renin level was more elevated ($p < 0.05$), and when renin secretion from the contralateral kidney was more suppressed ($p < 0.01$). The regression equations, just indicated, were not materially altered by excluding from analysis patients with bilateral lesions. The following variables did not contribute to the prediction of postoperative blood pressure: (1) the ipsilateral renal vein to arterial renin ratio[12]; (2) the ipsilateral to contralateral renal vein renin ratio[13]; (3) venous renin during captopril treatment[14]; (4) patients' ages; (5) surgical procedure used (either vascular reconstruction or nephrectomy); (6) and uni- or bilateral localization of the vascular lesions.

Performance of a scoring system[12] in predicting curability: Fourteen patients with unilateral renovascular disease, not receiving treatment at the start of the study, showed a simple correlation coefficient of 0.81 between the diastolic pressure during captopril administration and that after surgery. These patients were also assessed using the scoring system proposed by Vaughn et al.[12] A successful outcome was defined[12,15] as one in which the patients either achieved normotension or had a decrease in diastolic pressure of >75% to a level <110 mm Hg. Eight patients with a point score[12] ≥5 should have been good candidates for operation, but subsequent surgery improved[12,15] diastolic pressure in only 4. In addition, 2 of 6 patients with a score <5 became normotensive.

Discussion

The purpose of the present study was to compare the effects of long-term converting-enzyme inhibition with the results of surgery in hypertensive patients with renovascular disease and to evaluate the value of long-term captopril administration in predicting surgical outcome.

Comparison of results with converting-enzyme inhibition and surgery: Average blood pressure levels were similar during converting-enzyme inhibition and after surgery. This was true not only when all patients were considered together, but also when patients subjected to renovascular surgery or to nephrectomy or when patients with bilateral lesions were analyzed separately. Atkinson et al,[5,16] using captopril at a daily dose of only 450 mg, also reported successful inhibition of the plasma renin-angiotensin-aldosterone system and similar pressure levels during long-term converting-enzyme inhibition and after surgery in their patients with unilateral renal artery stenosis.

Preservation of renal function is an important consideration in the management of patients with renovascular disease.[17] Atkinson et al[16] recently reported that serum creatinine was not affected when patients, preoperatively treated with captopril, were followed up after nephrectomy ($n = 8$) or renovascular surgery ($n = 2$). In contrast, the present study demonstrated that the average serum creatinine and blood urea nitrogen levels were decreased after surgery as compared with captopril treatment. This observation may have clinical relevance. Renovascular hypertension is one of the major indications for converting-enzyme inhibition, and long-term captopril treatment may be considered as an alternative to surgical management. However, the present findings could suggest that patients with incipient renal insufficiency might benefit from an operation. However, the changes in creatinine clearance were not significant, and further studies using a smaller dose of captopril will be needed to clarify this issue.

Renin activity and endogenous angiotensin I levels remained high during converting-enzyme inhibition, but decreased after surgery when the patients were not on antihypertensive medication. Angiotensin II levels were similar pre- and postoperatively, but the angiotensin I to angiotensin II ratio declined strikingly, confirming that the converting enzyme was effectively inhibited during the preoperative period. Eighty percent of these measurements were made while the patients were taking a ceiling daily dose of 600 mg of captopril. However, some investigators[18] have reported that a single dose as small as 20 mg is able to block the pressor effect of exogenous angiotensin I for as long as 2.5 hours. Furthermore, in a chronic outpatient study we demonstrated that both the hypotensive effect and the inhibition of the plasma angiotensin II-aldosterone system plateau at a daily dose of 150 mg.[19] Therefore, the dose that we prescribed in the present study was greater than that required to inhibit the renin-angiotensin system. During captopril treatment agranulocytosis occurred in 1 patient,[20] but in no patient was proteinuria or a further impairment of renal function observed.

Urinary prostaglandins were measured in this study in view of recent evidence implicating a positive feedback mechanism between the opposing renin-angiotensin and kallikrein-prostaglandin systems.[21] Endogenous prostaglandins may also be involved in the hypotensive action of captopril.[22] However, no changes in urinary prostaglandins were found in patients subjected to renovascular surgery, whereas the decrease in urinary prostaglandin excretion, observed in patients with nephrectomy could merely reflect the reduction in renal mass by which these prostaglandins are synthesized.

With regard to blood pressure control, our results of surgical treatment seem somewhat less favorable than those reported in the literature.[12,17,23] However, our study differs from the others[12,17,23] in the patients' age distribution and in the proportion of patients with fibromuscular dysplasia (for example, 15% versus 36% in the Cooperative Study). The observation that blood pressure was smaller in our patients probably cannot be attributed to surgical failure, because patients undergoing nephrectomy had an anatomically successful procedure by definition, whereas in all patients subjected to renovascular surgery the patency of the renal artery or its bypass were verified angiographically.

Predictive value of long-term converting-enzyme inhibition: The blood pressure levels during converting-enzyme inhibition and after surgery were correlated. The first-order correlation coefficients indicated that the pressure level achieved by converting-enzyme inhibition explained by itself approximately one third of

the variability of the postoperative blood pressure. Atkinson et al[5] found somewhat higher correlation coefficients (0.74 [$p < 0.02$] for systolic and 0.68 [$p < 0.05$] for diastolic pressure), but only after the blood pressure distributions were transformed logarithmically, whereas in the present study the relation was not improved by such a transformation.

The value of long-term captopril therapy as a guide to surgical treatment was further evaluated in relation to other known predictors by stepwise multiple regression. This analysis indicated that blood pressure during converting-enzyme inhibition was the only significant predictor of systolic pressure after surgery. The multiple regression equation derived for diastolic blood pressure indicated that the hypotensive effect of surgery increased when blood pressure was lower during long-term converting-enzyme inhibition, when renin release from the contralateral kidney was more suppressed, and when circulating renin was more elevated during moderate sodium depletion. These 3 variables, known at the time of the operation, predicted postoperative diastolic pressure with an accuracy of 10 mm Hg in all but 4 of the present patients. The diagnostic value of contralateral renin suppression has been demonstrated previously,[12,24] whereas that of peripheral renin remains much debated. Several investigators have observed normal levels of renin and angiotensin II even in patients with proven renovascular hypertension.[25,26]

Hyperreninemia during long-term converting-enzyme inhibition, in contrast to that after acute angiotensin II receptor blockade,[14] did not contribute to the prediction of postoperative blood pressure. The same was also true for renin stimulation at the ipsilateral site, even when the presence of bilateral lesions was taken into account or when patients with bilateral lesions were excluded from analysis. This observation contrasts with other studies in which excessive renin secretion by 1 kidney was defined retrospectively in terms of the ipsilateral to contralateral renal vein renin ratio.[13]

When a scoring system[12] based on the relative difference between renal vein and arterial renin was used to predict surgical curability in initially untreated patients with unilateral stenosis, 57% of these patients were correctly classified as potential responders to surgery,[12] whereas diastolic pressure during converting-enzyme inhibition correctly classified (with respect to postoperative diastolic pressure) 81% of the 27 patients to within ±20 mm Hg and 52% to within ±10 mm Hg. Although pressure during long-term converting-enzyme inhibition appeared to be a better predictor of the outcome pressure than a baseline but untreated pressure, it must be admitted that we have not proven captopril to be better than a nonspecific hypotensive drug, and this comparison remains to be made.

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Nifedipine Tablets for Systemic Hypertension: A Study Using Continuous Ambulatory Intraarterial Recording

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The action of nifedipine tablets was examined in 17 patients with essential hypertension focusing particularly on the profile of blood pressure (BP) reduction over 24 hours resulting from both twice-daily and once-daily therapy (dose range 40 to 120 mg daily). This new formulation of nifedipine has a more prolonged and lower peak plasma level than an equivalent dose of nifedipine capsules. Our patients were fully ambulant and studied by continuous intraarterial recording techniques. BP responses during isometric and dynamic exercise testing were also observed. Within-patient comparisons of consecutive mean hourly systolic and diastolic BP showed a highly significant effect from twice-daily therapy ($p < 0.001$) for nearly the entire day. Also, significantly lower BP was maintained during isometric and dynamic exercise. Mean hourly heart rates were not significantly altered. The profile of action of the single morning dose was initially similar, but its efficacy diminished from 6 P.M. to 8 A.M. on the following day. Side effects were not unduly troublesome and did not cause any patient withdrawals. Four patients developed mild ankle edema. Two others had facial flushing.

Nifedipine given twice daily in tablet form, therefore, is an effective antihypertensive drug capable of lowering BP consistently over 24 hours in ambulant patients and during formal exercise testing. We suggest that this agent may be useful as initial therapy for systemic hypertension, although the tablets are not as yet widely available.

Nifedipine inhibits the inward flux of calcium ions across vascular smooth muscle and myocardial cell membranes. The vasodilatation that is produced may be observed in the coronary arteries but is predominant in the peripheral resistance vessels of the systemic circulation.[1] Hence this drug is not only useful in angina pectoris but also has potential as an antihypertensive agent. The effects of chronic treatment with nifedipine in hypertensive patients have previously been assessed using indirect methods of blood pressure (BP) measurement, mainly the standard mercury-in-glass sphygmomanometer.[2,3] The shortcomings of such methods have long been recognized, particularly the lack of information about BP during normal activities away from the hospital environment, throughout the day and night. Our aim was to study the profile of BP reduction over 24 hours resulting from nifedipine therapy in fully ambulant subjects by continuous intraarterial recording, using a new tablet formulation. This has slower release characteristics and produces lower peak plasma levels than the more familiar capsule formulation. We compared the action of once- and twice-daily therapy focusing particularly on any differences in the 24-hour control level of BP. We also examined the effects of twice-daily therapy on the response to a program of standardized physiologic tests to determine how the increase in BP induced by different forms of exercise was influenced by nifedipine.

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Methods

This was an open study of patients selected from the Harrow Hypertension Clinic. Since it has been shown that there are no placebo effects on intraarterial blood pressure recorded by the methods used in this study,[4] a placebo controlled

crossover trial design was considered unnecessary. Patients were considered for inclusion in the study if they had recently diagnosed untreated hypertension or if their BP was inadequately controlled on existing medication. Criteria for acceptance were mean BP recorded from 3 separate clinic visits >160 mm Hg systolic or >95 mm Hg diastolic (Korotkoff phase V), or both, using a standard mercury-in-glass sphygmomanometer. Each patient had a full clinical examination and laboratory screening tests to exclude secondary hypertension. No patient had greater than grade 2 hypertensive retinopathy or a blood urea level >10 mmol/liter. Five patients had clinical or electrocardiographic evidence of left ventricular hypertrophy. Before entry into the trial (marked by the date of the first intraarterial monitoring), all antihypertensive medication was withdrawn, so that all patients had been untreated for at least 4 weeks.

The technique of ambulatory BP recording has previously been fully reported.[5] Briefly, the patients were required to attend the hospital for percutaneous insertion of an intraarterial cannula into the brachial artery of the nondominant arm with use of local anesthesia. Cannulation was performed in the same area at each subsequent recording. The BP signal and the electrocardiogram from bipolar chest leads were recorded using a specially designed transducer/perfusion unit and a Medilog Mark I cassette tape recorder (Oxford Instruments). The latter also incorporated a time channel with an event marker. The equipment was lightweight and portable so that patients were fully ambulant and could carry out their usual daily activities, and sleep at home.

At the beginning of each study, after insertion of the cannula, each patient underwent a standard protocol of physiologic tests. This consisted of an initial 20-minute period of rest in the supine position, followed by head-up tilt to 60° (after warning) maintained for 5 minutes. Isometric exercise was then performed using a hand grip dynamometer for 2 minutes at 50% of maximum voluntary contraction. Any tendency to produce a Valsalva reflex was avoided by requesting the patient to count aloud. After a 2-minute rest period, each patient then performed continuous dynamic exercise on a bicycle ergometer with work loads increasing from 250, 400, 700 to 1,000 kilopond-meters (kpm) at 3-minute intervals. Exercise was stopped when requested by the patient. After a 5-minute recovery period in the supine position and equipment calibration, patients then resumed their normal daily activities, returning to the hospital only for equipment checks and recalibration, to allow for any signal drift (usually not more than 5 mm Hg), at about 12-hour intervals. Recordings were continued for 24 to 36 hours; the cannula was then withdrawn, hemostatis achieved, and the equipment removed.

Each patient was then started on nifedipine tablets, 20 mg taken twice daily at 8 A.M. and 8 P.M., increasing to 40 mg twice daily after 4 weeks if necessary, and subsequently to a maximum of 60 mg twice daily depending on clinic BP recordings taken at 2-weekly intervals. When clinic BP appeared optimally controlled and stable (usually after 2 to 3 months' therapy), a second intraarterial recording was performed exactly as just described.

Patients were then changed to a once-daily regimen of the same total dosage of nifedipine tablets taken at 8 A.M. and restudied without the exercise protocol of after a minimum treatment period of 4 weeks.

Analysis of data: The tape recordings were initially replayed and written out using a linear direct-writing recorder (Watanabe). This allowed assessment of the analog signal quality, and editing of any artifact. Consecutive hourly mean values of BP and heart rate were then obtained from each recording using a purpose-built hybrid analog/digital computer.[6] The hourly data from all patients were pooled for each consecutive hour of the day, and pre- and post-therapy differences assessed for statistical significance using Student's two-tailed t test on the paired results.

The supine rest, tilt, isometric, and dynamic exercise results were computed using a digitizing program. For supine rest, mean systolic and diastolic BP over 30 beats of each minute in the last 5 minutes was taken. During tilt, mean systolic and diastolic BP over consecutive 15-second periods from the start of the tilt to 1 minute after returning to the supine position, were computed. During isometric exercise, the mean systolic and diastolic BP over 20 beats every 30 seconds was computed and the peak response extracted from this assessment. For dynamic exercise the mean BP over 30 beats at the end of the final minute of each level of exercise was digitized for further analysis. For each test, heart rate values were extracted in the same way as BP. Pre- and post-therapy differences were again assessed using Student's paired t test.

Results

A total of 19 patients entered the study and underwent the first period of intraarterial monitoring. Out of this group, 2 patients were later withdrawn. One was unwilling to undergo the second recording and the other was admitted to hospital because of a small myocardial infarction. The latter patient had been on therapy for 15 weeks and had no history of ischemic heart disease. He made an uncomplicated recovery.

Of the 17 patients who underwent the first (untreated) and second (nifedipine tablets twice daily) intraarterial recordings, 11 were male and 6 female. Their mean age was 54.6 years (range 38 to 65) and their supine clinic BP (after 3 minutes' rest) was 182 ± 15/109 ± 9 (mean ± standard deviation). The mean interval between their recordings was 12.6 weeks (range 8 to 27). The mean dose of nifedipine tablets administered to this group was 80 mg daily.

Out of this group 8 patients consented to a third study while taking their previous total dose of nifedipine once daily in the morning at 8 A.M. One patient's results were not included for analysis because of technical problems (excessive transducer drift). The supine clinic BP of the remaining 7 patients was 186 ± 17.6/107 ± 9.4 (mean ± standard deviation). The mean interval between the second and third recordings was 9 weeks (range 6 to 14), and the mean dose was 80 mg daily.

Circadian variation and BP reduction over 24 hours: Mean hourly values of systolic and diastolic BP and heart rate were obtained consecutively throughout the day to assess the 24-hour profile of BP reduction. Figure 1 shows the group data from 12 noon on the first day of recording to the same time the following day, before and during therapy with nifedipine tablets, twice daily. The circadian variation of BP, which has previously been fully described,[7] is clearly shown.

Although the shape of the curve was unchanged by therapy, there was a substantial reduction in both systolic and diastolic BP throughout the 24-hour period. Within-patient statistical comparisons (paired t tests) showed the reduction in both systolic and diastolic BP to be highly significant ($p < 0.001$) for 23 of the 24 one-hourly periods. The heart rate was not significantly changed by twice-daily therapy throughout the 24 hours.

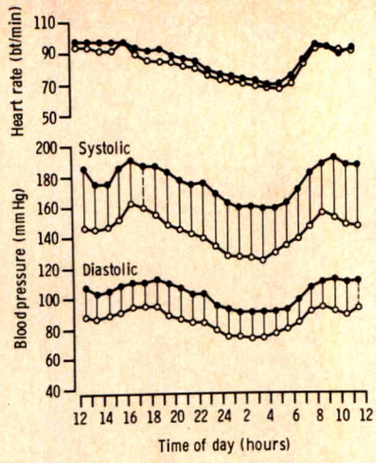

FIGURE 1. Circadian variation of heart rate and systolic and diastolic blood pressure in 17 patients. **Closed circles,** untreated; **open circles,** nifedipine tablets twice daily. Mean hourly differences: **solid lines,** p <0.001; **dashed lines,** p <0.01.

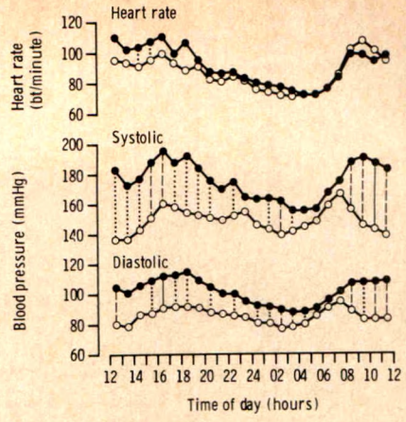

FIGURE 2. Circadian variation of heart rate and systolic and diastolic blood pressure in 7 patients treated with nifedipine tablets once daily (**open circles**). Closed circles, untreated. Mean hourly differences: **solid lines,** p <0.001; **dashed lines,** p <0.01; **dotted lines,** p <0.05.

Once-daily therapy (Fig. 2) produced a very similar profile of BP reduction from 9 A.M. until approximately 6 P.M. In fact, a slightly greater reduction was observed between 12 noon and 4 P.M. with once-daily therapy, although this was not statistically significant. However, between 6 P.M. and 8 A.M. on the following day the efficacy of the single dose was clearly diminished. The 24-hour heart rate profiles were almost identical, except for a small but significant increase in heart rate between 9 A.M. and 11 A.M. on the once-daily therapy.

Physiologic tests: A summary of the results is given in Table I. Fifteen patients provided satisfactory data for analysis; the remaining 2 patients had poor-quality recordings. A third patient was unable to perform dynamic exercise on the bicycle ergometer, so that results for this test were available in 14 patients.

The program began with a period of supine rest during which BP naturally tended to fall. Table I shows the group mean BP values taken from the last 5 minutes of supine rest. After treatment with nifedipine tablets twice daily, both systolic and diastolic BP were further reduced (p <0.001). During head-up tilt to 60°, BP was also significantly reduced by therapy (p <0.001), but there was no additional postural decrease in BP at the beginning of the tilt. Both untreated and treated heart rates increased slightly during the first 90 seconds of tilt. Peak values of systolic and diastolic BP obtained during isometric exercise were significantly reduced by therapy (p <0.001), although the rate of rise and the magnitude of the response was unaltered (Fig. 3).

There was no significant alteration in the peak heart rate response to isometric exercise. Systolic and diastolic BP was uniformly lower with nifedipine during each minute of dynamic exercise. The results are shown in Fig. 4 up to the ninth minute when 8 patients were still exercising. Again, the rate of rise and overall increase in BP was unaltered, and the heart rate response was also unchanged.

Side effects: There were no side effects considered severe enough to necessitate withdrawal from the trial. One patient was withdrawn after 15 weeks of medication because of a myocardial infarction; the circumstances of this were described earlier.

With twice-daily therapy, 3 patients developed ankle edema but had no change in body weight. Two others had flushing of the face and extremities almost 1 hour after each dose. One patient also complained of headaches and giddiness. During the once-daily treatment period 1 further patient developed ankle edema and another had headaches and giddiness.

Discussion

The only consistent hemodynamic abnormality in patients with essential hypertension is increased pe-

TABLE I Intraarterial BP During Physiologic Tests (Mean ± SD)

		Blood Pressure (mm Hg)	
		Before Treatment	After Treatment*
Supine rest (last 5 minutes) (n = 15)	Systolic	175 ± 20.5	141 ± 11.6
	Diastolic	98 ± 11.0	80 ± 8.0
Head-up tilt (60°) (n = 15)			
15 seconds	Systolic	174 ± 18.3	141 ± 17.0
	Diastolic	98 ± 8.6	81 ± 10.2
30 seconds	Systolic	179 ± 22.5	137 ± 16.6
	Diastolic	103 ± 12.5	81 ± 6.7
45 seconds	Systolic	175 ± 20.2	136 ± 11.71
	Diastolic	103 ± 11.6	81 ± 5.4
60 seconds	Systolic	175 ± 24.6	137 ± 12.6
	Diastolic	104 ± 11.9	83 ± 6.8
Peak isometric exercise (n = 15)	Systolic	230 ± 31.8	179 ± 20.2
	Diastolic	132 ± 20.4	103 ± 9.8
Peak dynamic exercise (n = 14)	Systolic	253 ± 25.1	209 ± 23.5
	Diastolic	139 ± 19.1	113 ± 13.2

* Significance of effect of treatment (paired *t* test) p <0.001 throughout.

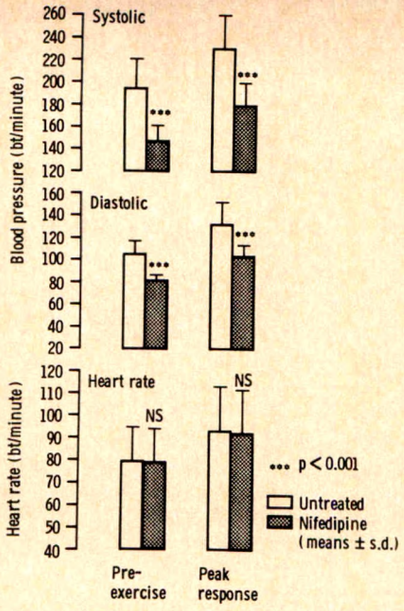

FIGURE 3. Peak blood pressure and heart rate responses to isometric exercise (means ± standard deviations [s.d.]) in 15 patients treated with nifedipine tablets twice daily. *** p <0.001; NS = not significant.

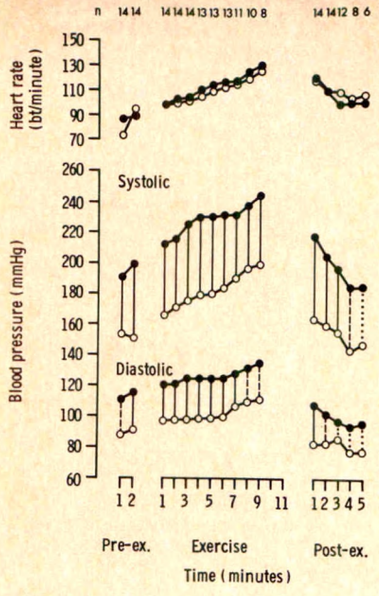

FIGURE 4. Heart rate and blood pressure responses to dynamic exercise in patients treated with nifedipine tablets twice daily (**open circles**). **Closed circles,** untreated. **Solid lines,** p <0.001; **dashed lines,** p <0.01; **dotted lines,** p <0.05.

ripheral resistance due to arteriolar vasoconstriction.[8] It is, therefore, logical that slow calcium-channel blocking agents, which relax vascular smooth muscle,[9] should be useful in treating this condition. Nifedipine has been reported to induce dilatation of the resistance vessels without affecting the venous capacitance vessels in normal subjects.[10] Also, a larger decrease in forearm vascular resistance in hypertensive patients than in normal subjects, after acute sublingual administration of nifedipine, has been described.[11]

The results of this study confirm the antihypertensive effects of nifedipine using direct methods of measurement. Furthermore, with the use of continuous ambulatory recording, during which patients have carried on their normal daily activities and slept at home, substantial BP reduction has been shown to occur throughout 24 hours with administration of nifedipine tablets twice daily. Once-daily morning therapy appeared effective for at least 12 hours after administration, after which control became poorer, as might be expected from the pharmacokinetic characteristics of nifedipine tablets.

The degree of antihypertensive activity we observed might be compared with that of beta-adrenoreceptor blocking agents. Similar studies with the latter agents have demonstrated that they may have little effect at night and during the morning period when BP is increasing rapidly.[12] This profile of action cannot be altered by varying the time of administration of the drug, or by using a multiple daily dosage regime instead of once-daily administration.[13] It has been suggested, therefore, that the rapid increase in BP in the morning follows a vasoconstricting sympathetic discharge mediated through alpha receptors in the peripheral arterial system. Although this remains to be proved, the effects of nifedipine, which is a potent vasodilator, contrast strongly with those of beta-adrenoreceptor blocking drugs.

In addition, nifedipine produced significant reduction in BP during the physiologic tests in the laboratory. During supine rest, untreated BP normally tended to decrease slowly to a steady baseline level. However, a further significant reduction in BP was observed with therapy. There was no postural hypotension at the onset of tilting. Absolute peak blood pressure levels were reduced by nifedipine, with no effect on the heart rate response during isometric exercise. These results are important because antihypertensive drugs have generally been disappointing in controlling BP elevations due to isometric exercise.[14] Similarly, absolute BP in response to dynamic exercise on a bicycle ergometer was significantly lower throughout the duration of the test, but there was no effect on the rate of change of BP with increasing work load or attenuation of the overall increase in BP. Comparable effects on BP during isometric and dynamic exercise have been reported with another slow calcium-channel blocking agent, verapamil,[15] and thus it is likely that these agents have no effect on the sympathetic reflexes responsible for these exercise-induced changes in BP.

It was interesting to note that mean hourly heart rate values were not significantly changed by chronic therapy. Acute studies with nifedipine capsules have shown a rapid decrease in BP with a concomitant increase in heart rate and cardiac output,[16] presumably due to a reflex increase in sympathetic activity mediated by the

baroreceptors. Differences between acute and chronic administration may be due to resetting of baroreceptor sensitivity, but it must also be taken into account that baroreceptor influences on heart rate may be short-lasting and have no significant effect on mean hourly heart rates. Other studies of chronic therapy for ischemic heart disease[17] have shown an increase in mean hourly heart rates, but in these studies nifedipine capsules were used, which produce high peak serum levels rapidly after each dose. The tablet formulation is less likely to do this.

Unwanted effects of vasodilator therapy such as increases in plasma noradrenaline or renin activity[18] and retention of sodium and water[19] have been reported; these effects could limit the BP reduction caused by nifedipine. They were not specifically quantified, but it appears from the BP reduction observed that these possible effects had no practical importance within the duration of this study.

In conclusion, therefore, nifedipine in tablet form has been shown to be an effective antihypertensive agent which can provide full 24-hour control with twice-daily dosage in ambulant patients and also maintain significantly lower BP during exercise. These results suggest that this drug may be useful as first-line therapy, although further studies are needed to establish its place in the long-term treatment of hypertension. The currently available nifedipine capsules are unlikely to produce the same results because of their shorter plasma half-life.

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Relation Between Site of Origin of Ventricular Tachycardia and Relative Left Ventricular Myocardial Perfusion and Wall Motion

THOMAS M. McFARLAND, MD, DAVID M. McCARTHY, MD,
P. TODD MAKLER, Jr., MD, and MARK E. JOSEPHSON, MD

To assess the relation between the site of origin of ventricular tachycardia (VT) and relative myocardial perfusion and wall motion, 18 patients with a history of recurrent sustained VT underwent cardiac catheterization, invasive electrophysiologic study with endocardial mapping, and resting radionuclide ventriculography. In addition, 6 patients had exercise and redistribution thallium-201 scintigraphy, whereas the remaining 12 patients had resting thallium scans. The site of origin of VT (determined by catheter and intraoperative endocardial mapping) was correlated with relative myocardial perfusion (thallium) and left ventricular (LV) wall motion. All patients had significant (>50% narrowing) coronary artery disease and 16 had LV aneurysms.

Twenty sites of origin of VT (28 morphologies) were identified in these 18 patients. Of the 9 patients with multiple VT morphologies, the VT originated at disparate sites in 2 patients. All 18 patients had thallium defects at rest and 3 patients had additional reversible (ischemic) defects on exercise. Of the 20 sites of origin of VT, 16 were at the periphery of the thallium defect, 1 was adjacent to it, and 3 were in the center of it. In the 16 patients with LV aneurysm, there were 18 sites of origin: 15 at the border of the aneurysm, 1 adjacent to it, and 2 within it.

The data suggest that in patients with VT and coronary artery disease the site of origin is usually the periphery of a resting thallium defect, and in patients with LV aneurysm the site is the border of the aneurysm.

Recurrent sustained ventricular tachycardia (VT) is a potentially lethal arrhythmia which is commonly associated with coronary artery disease, previous myocardial infarction, and left ventricular (LV) aneurysm.[1–3] Surgical therapy with coronary artery bypass grafting for recurrent VT has met with limited success, and LV aneurysmectomy has frequently failed to cure this arrhythmia.[3–8] More recently, LV aneurysmectomy coupled with endocardial excision at the site of origin of the recurrent VT (as determined by endocardial mapping) has been successful in the treatment of this arrhythmia.[8–11] Observations during LV aneurysmectomy, endocardial mapping, and endocardial excision suggest that VT generally originates at the border of a LV infarct scar.[10,11] To more objectively assess the relation between the site of origin of recurrent VT and relative myocardial perfusion and wall motion, catheter endocardial mapping of the site of origin of recurrent VT was compared with the results of thallium-201 myocardial perfusion scanning, radionuclide ventriculography, and coronary angiography and left ventriculography.

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Methods

Patient population: The study population consisted of 18 consecutive patients with recurrent sustained VT (Table I) who underwent endocardial mapping of the VT site of origin and thallium scintigraphy and radionuclide ventriculography. There were 17 men and 1 woman with a mean age of 56 years (range 39 to 73). All patients had significant coronary artery disease, defined as >50% diameter narrowing of a major cor-

TABLE I Clinical, Electrophysiologic Mapping, and Radionuclide Data in 18 Patients

Pt	Age (yr) & Sex	VT Site of Origin*	Surface ECG	Thallium-201 Defects		Wall Motion	Ejection Fraction (%)		Relation Between VT Site of Origin and:	
				Fixed (Scar)	Reversible (Ischemia)		RVG	Cath	Thallium Scar	Aneurysm
1†	73M	3–11	AS, Ant MI	Ant, S, Ap	. . .	Ant Ap AN	16	19	Center	Center
2	61M	2–3–5	LBBB	Ant, S, Ap	. . .	Ant Ap AN	9	19	Periphery	Border
3	60F	5	AS MI	Inf, Lat, Ap	. . .	Inf Ap AN	36	37	Periphery	Border
4†	61M	3–11	AS, Ant MI	Ant, Ap	Ant, S, Inf	Ant Ap AN	71	50	Periphery	Border
5	50M	5–6	Inf MI	Inf	None	Inf AK	38	43	Center	. . .
6	52M	6–8	Inf MI	Inf, Ap	. . .	Inf Bas AK	36	42	Periphery	. . .
7†	61M	11	AS, Ant, Lat MI	Ant, S, Ap	. . .	Ant Ap AN	30	42	Center	Center
8	50M	3–11	AS, Ant, Lat MI	Ant, S, Lat, Ap	. . .	Ant Ap AN	21	26	Periphery	Border
9†	63M	3–11	RBBB, AS MI	Ant, S, Ap	. . .	Ant Ap AN	26	40	Periphery	Border
10	39M	2–3–5	AS, Ant, Lat MI	Ant, S, Lat, Ap	. . .	Ant Ap AN	32	33	Periphery	Border
11	51M	2	AS, Ant, Lat MI	Ant, S, Ap	None	Ap AN	42	44	Periphery	Border
12†	41M	2–11	AS, Ant, Inf MI	Ant, Ap	. . .	Ant Ap AN	29	30	Periphery	Border
13†	45M	2‡ 9–11‡	AS, Ant, Lat MI	Ant, S, Ap	. . .	Ant S Ap AN	11	18	Periphery Periphery	Border Border
14	60M	6	Inf MI	Inf, Lat, Ap	. . .	Inf Lat AN	42	44	Periphery	Border
15†	66M	2–5‡ 11‡	RBBB, AS MI	Ant, S	Ap	Ant Ap AN	28	19	Periphery Periphery	Border Border
16	57M	9	AS, Ant, Lat MI	Ant, S, Ap	. . .	Ant Ap AN	28	30	Periphery	Border
17†	65M	6	LBBB	Lat	Lat, Ap	Inf Lat AN	39	35	Outside (adjacent)	Outside (adjacent)
18†	56M	8–10	Inf, Post MI	Inf, Ap	None	Inf AN	40	47	Periphery	Border

* Dashes indicate that ventricular tachycardia originated between the indicated sites.
† Multiple ventricular tachycardia morphologies.
‡ Disparate sites of origin.
AK = akinesia; AN = aneurysm; Ant = anterior; Ap = apical; AS = anteroseptal; Bas = basal; Cath = at catheterization; ECG = electrocardiogram; Inf = inferior; Lat = lateral; LBBB = left bundle branch block; MI = myocardial infarction; Post = posterior; Pt = patient; RBBB = right bundle branch block; RVG = by radionuclide ventriculography; S = septal; VT = ventricular tachycardia.

onary vessel, and 14 patients had total occlusion of at least 1 vessel. There were 4 patients with 1-vessel, 7 patients with 2-vessel, and 7 patients with 3-vessel coronary artery disease. Sixteen patients had a LV aneurysm at cardiac catheterization. The mean LV ejection fraction was 32% (range 9 to 71%).

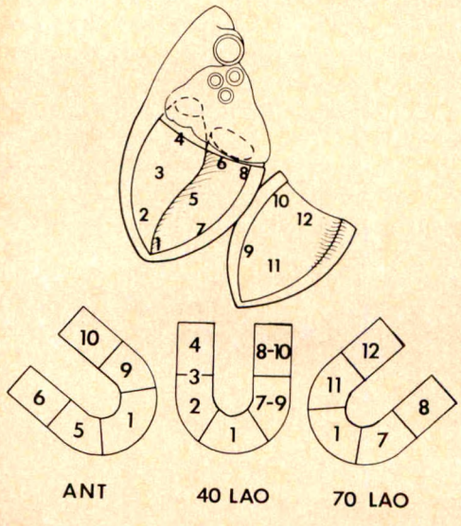

FIGURE 1. Top, schema of the 12 left ventricular endocardial mapping sites. **Bottom,** relation between the 12 left ventricular mapping sites and the thallium-201 scans in the anterior (ANT), 40° (40 LAO), and 70° (70 LAO) left anterior oblique views. See text for details.

Electrophysiologic studies: Electrophysiologic studies were performed in the nonsedated postabsorptive state. In each patient 3 to 6 electrode catheters were inserted either percutaneously or by cutdown and were fluoroscopically positioned in the right atrium, right ventricle, and left ventricle as previously described.[2,12] Programmed stimulation, including incremental ventricular pacing and introduction of 1 to 4 ventricular extrastimuli after every eighth spontaneous or paced beat, was performed with a programmable stimulator (Bloom Associates, Narberth, Pennsylvania). Current was delivered in 1.0 ms impulses at twice the diastolic threshold using an isolated constant current source.

Intracardiac electrograms were displayed simultaneously with 2 or 3 surface electrocardiographic leads on a switch-beam oscilloscope at filter frequencies of 30 to 500 Hz. Care was taken to assure electrical isolation of the patient and equipment. The data were stored on magnetic tape and later retrieved on photographic paper at speeds of 150 to 250 mm/s.

The LV mapping catheter was positioned using the retrograde arterial approach. The 12 preselected LV sites are shown in Figure 1. These sites include the LV apex (site 1), septum (sites 2 to 4), inferior (sites 5 and 6), inferolateral (sites 7 and 8), anterolateral (sites 9 and 10), and anterior walls (sites 11 and 12). When an aneurysm was present, mapping from the endocardial surface of the aneurysm was attempted. Catheter position was verified by fluoroscopy in multiple planes. Data were obtained by recording endocardial electrograms using an electrode catheter with a 1 cm interelectrode distance. Once the VT was initiated, endocardial mapping of the VT was performed.[12,13] Activation mapping from all 12 LV sites was obtained. Ventricular activation time at each LV site was determined by comparison with the right ventricular reference electrogram and the onset of the surface QRS complex. The

VT site of origin was defined as the site with the earliest activation. The accuracy of the activation mapping has been confirmed with intraoperative mapping of VT.[13,14]

Cardiac catheterization and contrast ventriculography: All patients underwent cardiac catheterization and selective coronary angiography by either the Sones or the Judkins technique. Left ventriculography was performed in the standard 30° right anterior oblique projection in all 18 patients, and a second ventriculogram in the 45° to 60° left anterior oblique projection was performed in 12 patients. The ventriculogram was analyzed by the area-length method in the right anterior oblique view for ejection fraction, and was studied qualitatively for LV asynergy including akinesis, hypokinesis, or dyskinesis.

Thallium-201 myocardial imaging: Resting thallium-201 imaging was performed in 12 patients who were deemed unable to exercise due to either poor LV function or recent femoral arterial catheterization or both. Left ventricular ejection fraction in these patients was significantly lower than that in the 6 patients who were able to exercise (27 versus 43%, $p < 0.02$). After injection of 1.5 to 2.0 mCi of thallium-201 chloride, images were recorded in the anterior, 40°, and 70° left anterior oblique views using a single crystal gamma camera (Picker Dynamo) interfaced to a dedicated nuclear medicine computer (DEC Gamma-11).

Exercise and redistribution thallium-201 imaging was performed in the 6 patients who were judged capable of performing an exercise test. The exercise test was performed on a treadmill using a modified Bruce protocol, and exercise was continued until the patient experienced anginal pain, fatigue, or lightheadedness. No patient had ventricular arrhythmia during exercise. Thallium-201 chloride (1.5 to 2.0 mCi) was injected approximately 1 minute before termination of exercise. Imaging began 10 minutes after the injection of tracer during exercise and was repeated 4 hours later for the redistribution scan. Images were acquired in the anterior, 40°, and 70° left anterior oblique views.

Radionuclide ventriculography: Radionuclide ventriculography was performed on a separate day by the equilibrium technique using red blood cells labeled in vivo with 20 mCi of technetium-99m pertechnetate.[15] All studies were performed during sinus rhythm with the patient supine, using a single crystal gamma camera. Scans were collected in the anterior and 45° and 70° left anterior oblique views. Ejection fraction was calculated from the 45° left anterior oblique scan.

Relation between a site of origin of VT and thallium scans: The relation between the 12 LV mapping sites and the thallium scans is shown in Figure 1. Each scan view was divided into 5 zones, and the perfusion defects were related to these zones. The scan graders were unaware of the results of endocardial mapping. Each scan zone correponds to 1 or more LV mapping sites. The site of origin of VT was said to be the *center* of a thallium defect if the scan zone corresponding to the site of origin and the scan zones of all contiguous mapping sites were involved by the defect. Ventricular tachycardia was said to originate at the *periphery* of a scan defect if the corresponding scan zone was involved by the defect but at least 1 contiguous mapping site was not involved in the defect. Finally, VT was said to come from a region *outside* a defect if the scan zone corresponding to the site of VT was not involved by the defect.

Relation between site of origin of VT and LV wall motion: Wall motion was elevated by 2 observers who were kept unaware of the other results. The extent of focal wall motion abnormality (akinesia or dyskinesia) was determined by superimposing the end-diastolic and end-systolic perimeters of the radionuclide ventriculogram with each view being divided into 5 regions (Fig. 2). Left ventricular wall motion also was assessed by contrast ventriculography. The results of both of these methods correlated well (Table I) and were both used to define the presence and location of LV aneurysms. Left ventricular ejection fraction using both methods correlated closely ($r = 0.82$).

Large regions of discrete LV akinesia or dyskinesia were interpreted as indicating the presence of a LV aneurysm. The site of origin of recurrent sustained VT as determined by endocardial mapping was then compared with LV wall motion, using the relation shown in Figure 2. In patients with a LV aneurysm, the site of origin of VT was assessed as to whether it was on the border, in the center, or outside of the LV aneurysm, using a similar schema as with the thallium-201 scans.

Results

There were 28 morphologically distinct VT in the 18 patients, and these were localized to 20 sites of origin (Table I). In 2 patients (Patients 13 and 15) with 2 VT morphologies each, the origins occurred at disparate sites. Ten sites of origin of VT involved the septum of the left ventricle, 6 sites of origin the inferior region of the left ventricle, and 4 sites of origin the superior LV free wall.

All 18 patients had abnormal thallium scans at rest or redistribution (fixed defects), and 3 of the 6 patients with exercise scans had additional (ischemic) defects on exercise. The peak heart rate of the 3 patients with ischemic defects on exercise was 83% of predicted maximum versus 64% for the 3 patients who did not demonstrate ischemic defects with exercise. Of the 20 sites of origin of VT, 16 were the periphery of the fixed defect and 3 were the center of the fixed defect. In only 1 patient (Patient 17) was the site of origin of VT thought to be outside the fixed thallium defect. In the 3 patients with additional ischemic perfusion defects on exercise, the site of origin of VT was located in the fixed (redistribution) defect and not in the reversible (ischemic) defect.

Sixteen of the 18 patients had a LV aneurysm. Of the 18 sites of origin of VT in these patients, 15 were thought to be the border of the aneurysm and 2 within the aneurysm. In only 1 patient (Patient 17) was the site of VT thought not to be the border or within the aneurysm, and in that 1 patient the site of VT was adjacent to the aneurysm.

Figure 3 shows the results in a 39-year-old man (Patient 10) with a history of anteroseptal and anterolateral myocardial infarction and recurrent sustained VT. All 3 views of the resting thallium scan show extensive scar,

FIGURE 2. Relation between the 12 left ventricular mapping sites (see Fig. 1) and the radionuclide ventriculograms in the anterior (ANT), 45° (45 LAO), and 70° (70 LAO) left anterior oblique views. See text for details.

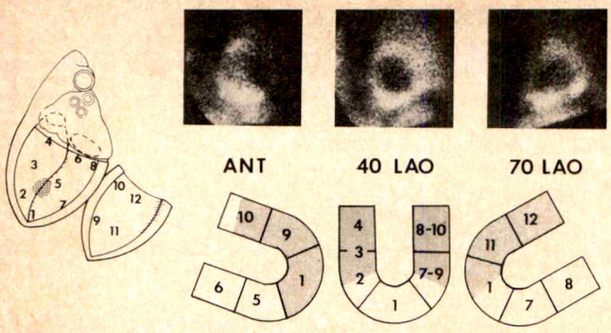

FIGURE 3. Resting thallium-201 scans (**right**) in Patient 10. The location of the perfusion defects is indicated schematically below the scans. The patient's ventricular tachycardia originated at the junction of the mid-septum and the inferior wall, shown by the stippling on the schema (**left**). See text for details.

with the defect indicated schematically below. The earliest site of ventricular activation during VT in this patient was the point at which the mid-septum meets the inferior wall (between sites 2, 3, and 5) and is depicted by stippling on the schematic mapping diagram in the illustration. The site is the periphery of the thallium defect, since the scan defect involves sites 2 and 3 (septum) but not site 5 (the contiguous site). The site of origin of VT was also the border of an anterior aneurysm seen on both the radionuclide and the contrast ventriculogram.

Discussion

The mechanism of recurrent sustained VT in man is believed to be reentry from a relatively small and protected region of the heart.[2,16,17] Catheter mapping suggests that reentry takes place at or near the endocardium.[12,16,17] Epicardial mapping has previously been used as a guide to surgical therapy for recurrent sustained VT; however, studies in both animals and man show that the endocardial site of origin of VT may be distant from the site of epicardial electrical breakthrough.[14,18] Early surgical results of endocardial mapping and endocardial excision have been encouraging.[8–11] Observations during LV aneurysmectomy, endocardial mapping, and endocardial excision have suggested that the site of origin of recurrent VT is generally the border of a LV myocardial infarction scar.[10,11]

Limitations of methods: The accuracy of endocardial catheter determination of the site of origin of recurrent sustained VT has previously been validated with intraoperative endocardial mapping.[13,14] Endocardial catheter mapping of VT can predict the site of origin of VT within 4 to 8 cm^2 of that determined by intraoperative endocardial mapping.[9,10,13] Furthermore, the accuracy of endocardial catheter activation mapping in this study was confirmed with intraoperative mapping during sustained VT in 16 of the 18 patients.

Left ventricular wall motion was analyzed by both radionuclide ventriculography and contrast ventriculography, with good correlation of wall motion and ejection fraction by both methods. This finding is in agreement with those of previous studies.[19] The complementary use of these methods provided good identification and localization of LV aneurysms, as expected from previous reports.[20]

The analysis of myocardial perfusion in this study was obtained from the results of thallium-201 myocardial scintigraphy, which provides a visual representation of the relative distribution of myocardial blood flow. In this group of patients, resting or redistribution thallium-201 myocardial perfusion scans revealed relatively large defects associated with previous myocardial infarctions which were suspected from the patients' histories and electrocardiograms. Thallium defects reflect both the site and the location of myocardial infarction,[21,22] although small infarcts (<7 g) may not be identified.[23] Phantom studies[24] have shown that defects as small as 1.5 cm in diameter can be detected, although defects are probably more easily identified in a phantom study than in a patient.[23] The consistent finding that the site of origin of VT is the periphery of the thallium scan defect and the border of the LV aneurysm lends further support to the reliability of the method.

Exercise-induced perfusion abnormalities: To assess the possible correlation between myocardial ischemia and the site of origin of recurrent VT, exercise thallium-201 myocardial perfusion scanning was performed in those patients who were judged capable of exercising. Only 6 of the 18 patients were able to undergo thallium-201 exercise myocardial perfusion scanning, and of these 6 patients, only 3 patients had reversible perfusion defects with exercise. In these 3 patients, 3 of the 4 sites of origin of VT were the periphery of the fixed defect. Importantly, VT was induced by programmed extrastimuli in the *absence* of ischemia, and the development of ischemia during exercise was *not* associated with the appearance of VT. Although the number of patients is small, these results suggest that ischemia may not be a major factor contributing to recurrent VT in these 3 patients. This impression is further supported by a recent preliminary report in which 25 patients with recurrent sustained VT underwent treadmill testing and only 2 of the 25 patients developed VT on exercise.[25]

Pathophysiology: The finding that the site of origin of recurrent VT is the periphery of a myocardial infarction scar is consistent with the requirement that a segment of tissue that is electrophysiologically excitable be adjacent to one of slow conduction. Myocardial infarction scar tissue is typically associated with abnormal conduction.[26,27] The border zone of the myocardial infarction scar has a heterogeneous transition zone from homogeneous fibrous scar tissue to normal myocardium, and thus provides an electrophysiologic substrate for the origin of dysrhythmia. Preliminary data suggest such an anatomic substrate.[28] Because 16 of the 18 patients with recurrent VT had a LV aneurysm involving the site of a previous large myocardial infarction, increased wall tension in the border zone of the LV aneurysm may also have a role in producing recurrent VT.

Clinical implications: The results of this study support the intraoperative observations that the site of origin of recurrent VT generally is the border of a LV

aneurysm or the periphery of a LV myocardial infarction scar.[10,11] These results help to explain previous limited surgical success in the treatment of recurrent VT by coronary artery bypass grafting and LV aneurysmectomy, because LV aneurysmectomy usually does not remove the border region of the LV aneurysm, particularly in patients with VT arising from the ventricular septum. Thus, the present study provides noninvasive support for endocardial excision of the site of origin as an essential component in the surgical treatment of recurrent VT.

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Ultrarapid Single-Capture Train Stimulation for Termination of Ventricular Tachycardia

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SOO GYUM KIM, MD, and JEFFREY A. MATOS, MD

Termination of ventricular tachycardia (VT) with single programmed extrastimuli or slow underdrive competitive pacing is often possible. The usefulness of these techniques is limited because the zone in the cardiac cycle during which programmed stimuli are effective may be narrow, with significant time elapsing until termination of the VT, and the zone may vary markedly between episodes, rendering preset extrastimuli ineffective. Ultrarapid trains of stimuli beginning during the refractory period and of a duration sufficient to cause only a single capture should terminate all tachycardias whose termination zone begins just after the refractory period. To test this hypothesis, 21 patients with 371 well-tolerated episodes of VT had single programmed extrastimuli and trains of 10 bipolar stimuli at 25, 50, and 100 Hz. VT was terminated 1 or more times in 18 of the 21 patients with programmed extrastimuli or trains, or both. Forty-eight percent of 290 episodes were terminated with programmed stimulation, compared with 56% of 120 episodes with trains (difference not significant). In 98 episodes, the effects of trains and programmed stimulation could be matched (same patient, date, tachycardia morphology, rate, and drug therapy); the results were concordant (both techniques either terminated the VT or failed) in 92 and discordant in 6. With only 2 possible exceptions, the termination zone always began just after the refractory period; thus, for tachycardias terminating with single captures, the first train to achieve capture was effective, minimizing the duration of the VT.

Ultrarapid train stimulation at rates equivalent to several thousand beats per minute, but with the duration of the train limited to achieve only a single capture, has been used with high stimulus amplitudes in the study of ventricular fibrillation thresholds[1,2] and at lower amplitudes for the termination of supraventricular tachycardias.[3] Termination of ventricular tachycardia (VT) with single programmed extrastimuli is often possible[4–8] but is of limited use in implantable pacemakers because the zone in the cardiac cycle in which programmed stimulation is effective (termination zone or window) may be narrow with significant time elapsing until termination; and the zone may vary daily,[8] rendering preset[6,7] extrastimuli ineffective. However, if the termination zone begins just at the end of the refractory period, train stimulation at 50 to 100 Hz beginning in the refractory period, and of a duration causing a single capture, should terminate all susceptible tachycardias, unaffected by changes in the timing and duration of the termination zone (Fig. 1). The present study tests this hypothesis, and determines whether high-frequency train stimulation might be useful in the termination of VT.

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Methods

Twenty-one patients undergoing serial electrophysiologic testing for control of recurrent VT were studied. Patients were selected for participation in the train stimulation study if the VT was sufficiently well tolerated to permit detailed testing with the extrastimulus technique and with train stimulation.

The 21 patients included 16 with coronary artery disease, 2 with dilated cardiomyopathy, and 1 each with mitral valve prolapse, arrhythmogenic right ventricular dysplasia, and no demonstrable heart disease. There were 15 men; ages ranged between 18 and 78 years (mean 58).

After induction of VT and establishment of hemodynamic stability, attempts at termination were begun. Single programmed extrastimuli or 100 Hz train stimulation were used as described later, in alternating sequence for successive episodes or termination attempts. Programmed stimulation was initiated beginning within the refractory period (130 to 150 ms after sensing of the VT beat) and moving later in 10 ms steps. Programmed extrastimuli were given every eighth beat, and continued until termination of the VT, or until the entire diastolic period was scanned. Similarly, during established VT, trains of 10 bipolar stimuli were delivered every eighth VT beat, beginning in the refractory period. Intervals between successive stimuli in the train were 10 ± 2 ms (100 Hz, 6,000 beats/min) in all 21 patients. Trains with intervals approximating 20 and 40 ms (50 and 25 Hz) were subsequently used in 17 and 11 patients, respectively, and 3 to 5 ms interval trains were used in 3 subjects.

Programmed extrastimuli and train stimulation used in the attempted termination of the VT were provided by a Savita Orthorhythmic® pacemaker. This device is designed to sense with the stimulating catheter, using typical pacemaker type signal processing. The unit is powered by 2 large capacity

batteries. Stimulus amplitudes remained constant during trains at up to 10 mA, and from 11 to 14 mA the delivered stimulus amplitude decreased by a maximum of 15% by the last stimulus in the train. In 4 patients, the stimulus amplitude was set at 4 times diastolic threshold; in the remainder, all stimuli were delivered at 10 to 14 mA, representing >4 times threshold.[9] Each stimulus was 1 ms in duration. The same settings were used for extrastimuli and for trains in each patient.

For 100 Hz trains, the first stimulus was delivered with a delay of 50 ms after sensing of the QRS complex, with the resulting train therefore covering the zone from 50 to 150 ms (always within the refractory period in these patients). Thereafter, the timing of the train was delayed by an additional 10 ms after every eighth VT beat, until capture was obtained or diastole was scanned. With 50 and 25 Hz trains, stimulation began simultaneously with sensing of the QRS complex. Some 50 Hz trains ended within the refractory period, and in such cases the timing was sequentially delayed as for 100 Hz trains.

In patients with easily reproducible VT, the effects of programmed stimulation and train stimulation were confirmed over several trials. The outer limit of the termination zone was established with use of programmed stimulation beginning late in diastole and then with increasing prematurity in 10 ms steps. During testing for reproducibility of termination, the timing of 100 and 50 Hz trains was set to exceed the refractory period by 30 to 40 ms. In comparing trains of different frequency, 100 Hz trains were used first, followed by 50 and 25 Hz.

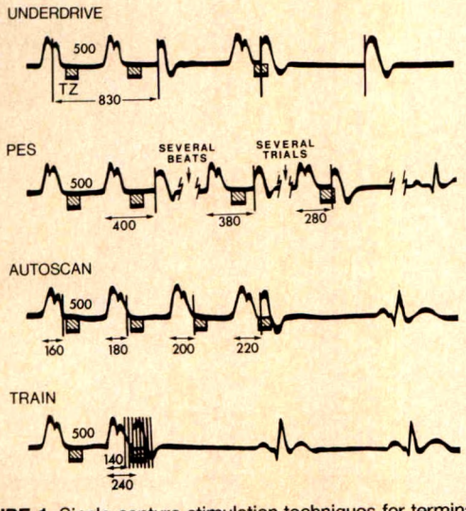

FIGURE 1. Single-capture stimulation techniques for termination of VT. In each panel, VT with a cycle length of 500 ms is illustrated schematically, with the termination zone (TZ) represented by the **hatched box** following the QRS complex. **Top panel,** underdrive. Pacing stimuli appear asynchronously at an arbitrary 830 ms, eventually capturing during the termination zone. This technique is highly inefficient if the termination zone is narrow, or if the tachycardia is poorly tolerated. Further, if the tachycardia rate is a multiple of the underdrive pacing rate, stimulation may occur isorhythmically, never hitting the termination zone. **Second panel,** programmed electrical stimulation (PES). Programmed extrastimuli are inserted every several beats, with their timing altered with respect to the previous QRS complex. Systematic stimulation throughout the diastolic period will ultimately find the termination zone. Programmed extrastimuli are usually begun late in diastole, and then with regularly increasing prematurity. In the present study, the extrastimuli were begun during the refractory period, with subsequent incremental delays. **Third panel,** autoscan. Several varieties of automatic scanning pacemaker techniques have been described. In this variation, the extrastimulus is begun during the refractory period and each QRS complex is followed by a slightly more delayed extrastimulus, until the termination zone is reached. **Bottom panel,** train stimulation. A train is initiated during the refractory period, with the duration sufficient to result in a single capture. Because the tachycardia termination zone begins at the end of the refractory period, termination occurs with the first train.

Refractory periods were measured from recordings made at a paper speed of 100 ms by an Electronics for Medicine VR6 or VR12, or by an Elema Mingograf. The following definitions were used: V_1 = VT beat; V_2 = programmed extrastimulus; and V_{11} = final stimulus in a 10 stimulus train. The effective refractory period was the longest V_1-V_2 or V_1-V_{11} failing to capture.

The functional refractory period was equal to the shortest attainable interval between V_1 and the beat resulting from V_2 or V_{11}. Capture could occur in the midst of a train (typical for 25 and 50 Hz trains and during testing of reproducibility with 100 Hz trains). The functional refractory period was then estimated by measuring from landmarks (Fig. 2, B and D) on the stimulated QRS complexes, and comparing the timing of these with similar landmarks in beats produced by a single extrastimulus at the shortest V_1-V_2 resulting in capture.

When possible, episodes of VT "matched" for date, medications, rate, morphology, and so on were compared. For refractory periods, effective refractory periods were used if available; if not, functional refractory periods from both extrastimuli and trains were compared.

The relative effectiveness of programmed stimulation and train techniques were compared using chi-square analysis. The refractory periods obtained with programmed and train stimulation were compared using a paired t test in episodes matched for patient, date, tachycardia morphology, rate, and medications.

Results

Three hundred seventy-one episodes of VT were studied; the number of episodes was 3 to 82 per patient. Three to 10 episodes were studied in 8 patients, 11 to 20 episodes in 6 patients, 21 to 30 episodes in 4 patients, and ≥34 episodes in 3 patients. VT rates were 106 to 171 beats/min, with a mean of 124 (cycle length 484 ms).

Relative efficacy of programmed stimulation and trains (Fig. 2 and 3): There were 98 matched episodes (same patient, date, VT morphology, and medications) for direct comparison of the extrastimulus and train techniques. There was a concordant response in 92 of these episodes: 38 could not be terminated by programmed stimulation or trains, and 27 were terminated by programmed stimulation and 27 by trains. There was a discordant response in only 6 episodes, 4 of which were terminated by trains but not programmed stimulation, and the reverse for the remaining 2 episodes. Overall, 139 (48%) of 290 episodes were terminated by single programmed extrastimuli, and 67 (56%) of 120 episodes by trains (difference not significant). The total number of episodes appears to exceed 371 because some individual episodes were treated with both programmed extrastimuli and trains.

When trains were used for successive episodes, the train was timed to straddle or bracket the previously determined refractory period, so that 20 to 30 ms fluctuations in the refractory period would be encompassed. On similar reproducibility trials with programmed extrastimuli, the greater time required for termination was often dramatic (Fig. 3).

Thirty-two pairs of refractory periods from pro-

grammed and train stimulation were compared in matched VT episodes in 20 patients. The refractory periods with trains (333 ± 112.5) were found to be 11 ms longer ($p < 0.02$) than with single extrastimuli (322 ± 110). Because the time from onset of VT to termination could not be controlled, it is not clear whether the differences in refractory periods were due to the stimulation techniques themselves, or to secondary changes (such as changes in autonomic tone related to the duration of the arrhythmia).

With both programmed stimulation and trains, the termination zone, when present, began immediately after the effective refractory period, with only 2 possible exceptions outlined in the next paragraph. The duration of the termination zone was assessed in 20 episodes from 11 subjects using the single extrastimulus method. The termination zone varied from 0 to 300 ms (mean ± standard deviation 91 ± 70). A value of zero was recorded when termination was possible only at a single setting established by 10 ms steps, as described in the Methods section.

Comparison among 100, 50, and 25 Hz trains: Among 18 patients tested, the responses to 25 or 50 Hz trains were found to be concordant with those of 100 Hz

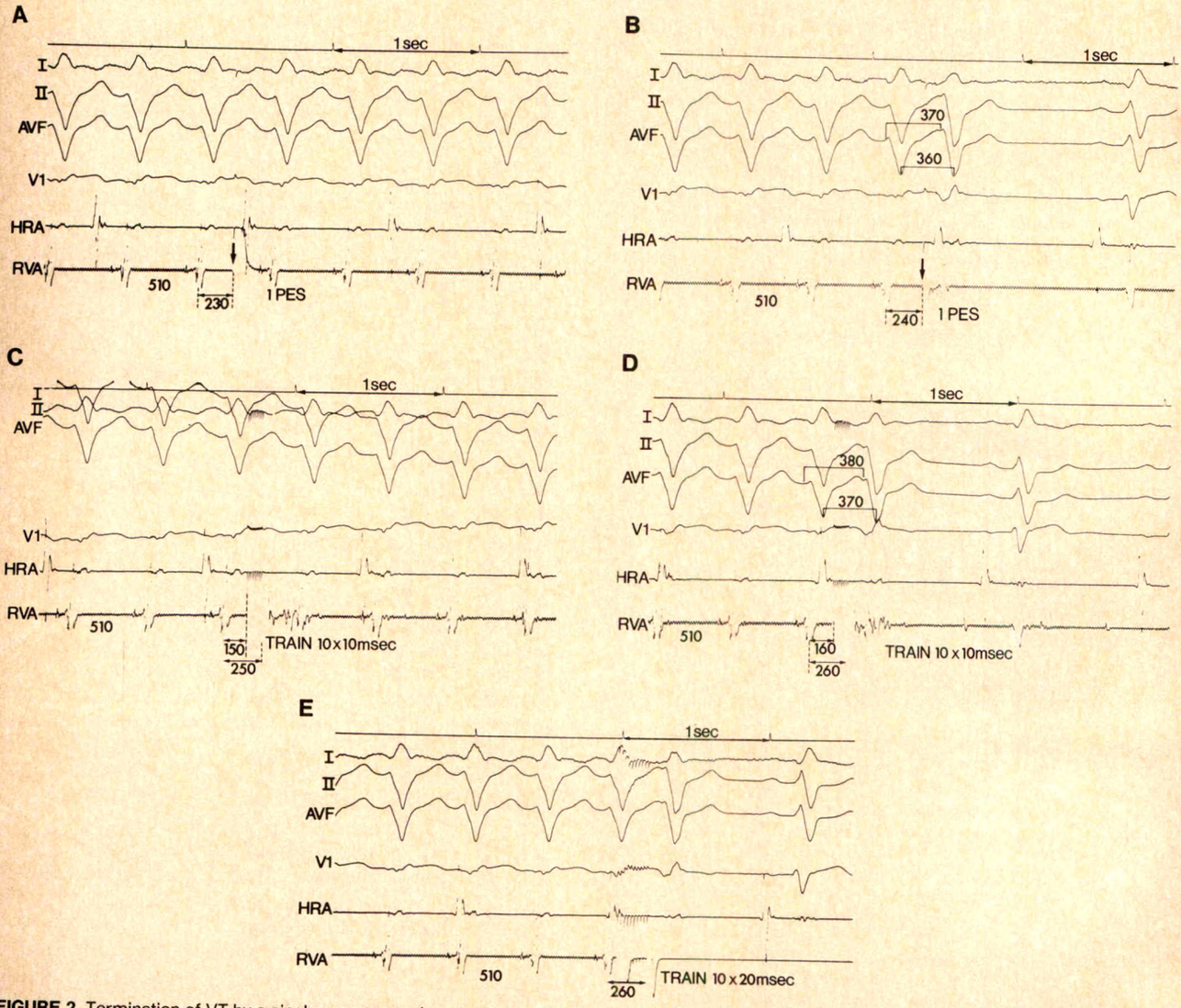

FIGURE 2. Termination of VT by a single programmed extrastimulus (PES) and train stimulation. These illustrations are taken from the same patient, during "matched" episodes of VT as described in the text. In each, the format is the same, with peripheral leads I, II, AVF, and V_1 displayed, together with electrograms from the high right atrium (HRA) and the right ventricular apex (RVA). **A,** a single PES 230 ms after sensing of the QRS complex fails to capture the ventricle. **B,** a single PES delivered 240 ms after sensing of the QRS complex captures the ventricle and terminates the tachycardia. The measurements shown in AVF illustrate the type of "landmarks" used to estimate refractory periods with 20 and 40 ms (50 and 25 Hz) trains (see text). **C,** a 10 ms (100 Hz) train begun with a delay of 150 ms after sensing of the QRS complex fails to capture the ventricle. **D,** the delay of the train is increased to 160 ms, with capture of the ventricle and termination of the tachycardia. The settings on the stimulator, and measurements from both the right ventricular apex and the landmarks in AVF measured in **B** all confirm the refractory period and the termination zone with trains beginning approximately 10 ms later than with PES. **E,** a 20 ms (50 Hz) train began 60 ms after sensing of the QRS complex, and terminates the tachycardia in a fashion similar to that observed with PES and 10 ms (100 Hz) trains. These tracings were all recorded during serial antiarrhythmic trials several days after the initial study. Tachycardias of a similar configuration were observed during the initial study, and His bundle potentials were not observed before the QRS complex, nor was there other evidence to suggest a diagnosis other than VT. The small deflection before the right ventricular apex complex may represent bundle branch activity, "fractionation," or far-field effects.

trains in 44 matched episodes (Fig. 2, D and E) and discordant in 4: 2 were terminated by 100 Hz, but not 50 or 25 Hz trains; 1 episode unresponsive to 100 Hz trains was terminated by a 50 Hz train; and 1 episode unresponsive to programmed stimulation, as well as 100 and 50 Hz trains, was terminated by a 25 Hz train. Whether these were due to fluctuations in the termination zone or other factors related to prior stimuli (see later) is uncertain. Three of the 18 patients also received trains with a cycle length of 3 to 5 ms (330 Hz, 200 Hz)

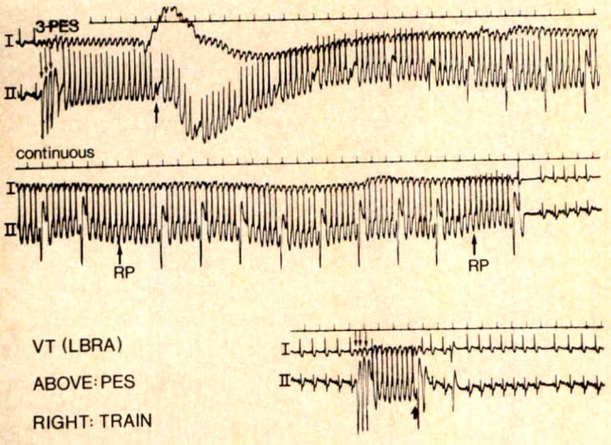

FIGURE 3. Programmed stimulation and trains contrasted. Peripheral leads I and II are displayed along with 1 second time lines. Ventricular tachycardia (VT) of a left bundle right axis morphology (LBRA) is induced by triple programmed extrastimuli (PES), indicated by the 3 **small downward-pointing arrows.** The **top 2 panels** represent a single episode. Attempts to terminate with use of a single PES begin at the **large upward-pointing arrow.** These episodes were recorded in a patient studied after those patients reported on in the present study and incorporate minor changes in the protocol based on lessons learned. The PES are given after every sixth beat, with 20 ms decrements until the effective refractory period (RP) is reached. At that point, the PES is delayed by 40 ms, and then moved once again toward the refractory period in 10 ms steps. The refractory period is not reached for the second time until the ninth stimulus, because of operator inertia and the few seconds required to reset the controls. The tachycardia is finally terminated by an extrastimulus 10 ms beyond the effective refractory period. Time from induction to termination of tachycardia was 70 seconds. **Lower panel,** an identical tachycardia is induced, and terminated by the first 100 Hz train within 4 seconds. The orthorhythmic pacer is limited is 10 stimuli per train. A more flexible device able to generate 15 stimuli would have reached the refractory period (and potential termination zone) of all tachycardias observed in this series with an interstimulus interval of 10 ms and a delay of 150 ms after the previous QRS complex.

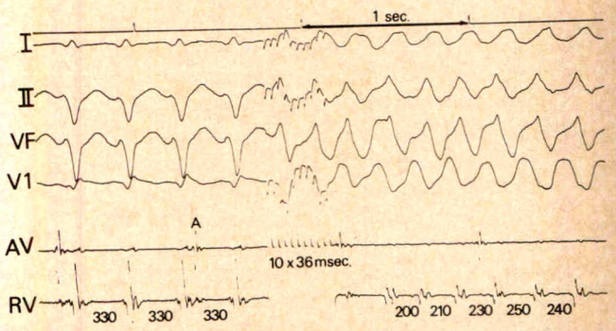

FIGURE 4. Acceleration of VT by a train resulting in 2 captures. Format as in Figure 2. A train with an interstimulus distance of 36 ms is initiated late enough so that 2 ventricular captures result, and accleration ensues. During this study, 20 and 40 ms (50 to 25 Hz) trains were usually initiated with minimal delay after the QRS complex to avoid double capture. AV = lead recording low right atrium and right ventricular inflow; RV = right ventricle.

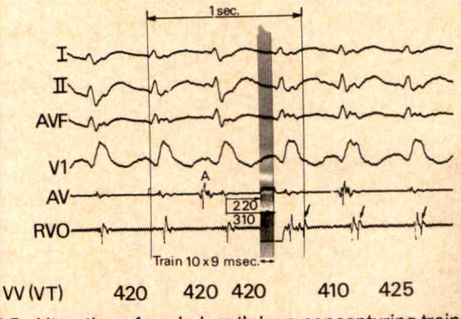

FIGURE 5. Alteration of cycle length by a noncapturing train. Format as in Figures 2 and 4. Ventricular cycle lengths during ventricular tachycardia (VV) (VT) are recorded at the **bottom** and were stable. After 3 regular complexes, an apparently ineffective train is followed by transient alterations in the cycle length, suggesting the possibility that some local capture or fusion did in fact occur. A = atrial depolarization; RVO = right ventricular outflow. Other abbreviations as in Figure 4.

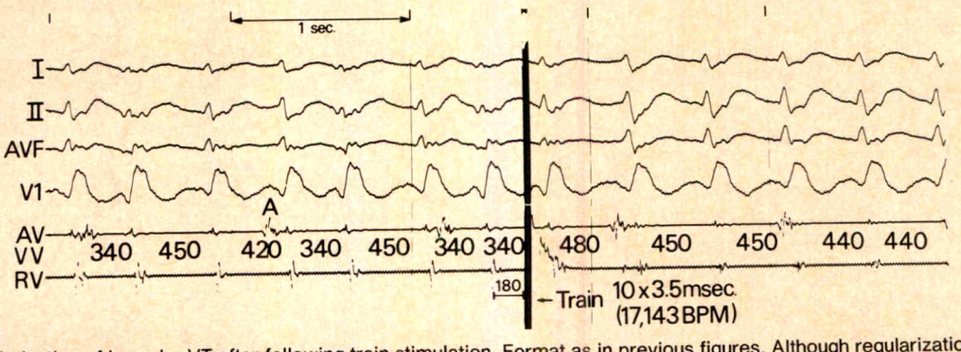

FIGURE 6. Regularization of irregular VT after following train stimulation. Format as in previous figures. Although regularization of a tachycardia may occur spontaneously, its appearance after an otherwise apparently ineffective train once again suggests the possibility of localized depolarization. This patient had tachycardias of several morphologies, with differing initial sites of ventricular depolarizations as determined by intracardiac mapping studies. There were instances of apparent "simultaneous VT"; the illustrated episode (not mapped) may have been such a multitachycardia as judged by the varying morphology of the complexes in leads I and II. One interpretation of the observed changes would be that the train terminated 1 of these tachycardias, regularizing both the cycle length and the morphology. BPM = beats per minute; other abbreviations as in Figures 4 and 5.

during 17 episodes, with results concordant with 100, 50, and 25 Hz trains.

Three episodes of VT were accelerated by train stimulation. Two occurred with a 25 Hz train (10 × 40 ms = 400 ms duration), which resulted in 2 captures (Fig. 4); 1 episode required direct-current cardioversion; the other was unsustained. One episode was accelerated by a 100 Hz train, and 1 by a single programmed extrastimulus. Overall, only 2 (0.54%) of 371 episodes of VT were accelerated by single-capture stimulation.

Other observations: Programmed and train stimulation failed to achieve capture during 7 episodes of VT, despite an adequate threshold margin before and after the episode and successful termination by conventional burst pacing[10] (Fig. 5 and 6). These figures also illustrate the possibility that train stimulation without capture may exert electrophysiologic effects. In Figure 5, the cycle length of a regular VT is altered, and in Figure 6 (the same patient as in Figures 4 and 5), the irregular tachycardia becomes regular after an otherwise ineffective train. In other episodes, the noncapturing train had no effect on cycle lengths.

Discussion

Ultrarapid single capture train stimulation for termination of VT offers several potential advantages. Because the termination zone begins at or very near the end of the refractory period, trains beginning within the refractory period and of a duration calculated to result in a single capture should immediately terminate susceptible VT, despite any changes in refractory periods from day to day or under various metabolic or antiarrhythmic drug conditions.[8]

The risks of acceleration with single capture stimulation (0.54% in this series) appear smaller than those with multicapture techniques.[8–11] Nevertheless, ventricular stimulation in patients with ventricular arrhythmias must always be approached with caution and respect. The potential hazards of train stimulation are evident from its heritage as a test of ventricular fibrillation thresholds,[1,2] and in this study 2 episodes were accelerated by trains of sufficient duration to cause 2 captures. Most VT susceptible to single-capture termination is rather slow (124 beats/min in this series).[8] Faster VT often requires multicapture stimulation methods for termination, with an attendant increase in risk of acceleration.

"Underdrive pacing" in which asynchronous pacer stimuli are delivered randomly during VT[12] may require considerable time for termination of susceptible tachycardias. Automatic "scanning" pacemakers[5–7] deliver programmed extrastimuli in an orderly fashion, but may still require multiple trials. Even pacers with a "memory"[6,7] for the timing of effective stimulation are problematic if the termination zone is narrow and changes significantly from day to day.

As judged from single programmed extrastimuli, the termination zone when present begins immediately after the refractory period. Whereas this was almost always true for train stimulation, there were 2 episodes in which 25 or 50 Hz trains terminated the arrhythmia, while 100 Hz trains were ineffective. In 1 of these episodes, single programmed extrastimuli had also failed to affect the tachycardia. Spontaneous alterations in threshold or tachycardia zone may have played a role in these anomalies, but effects of stimulation during the refractory period have been recognized since 1926.[13,14] More recent work has identified a variety of responses to single, multiple, and train stimulation within the refractory period, with complex interpretations related to summation, inhibition, temporal dispersion of refractoriness,[15] and electrotonic interactions.[16]

The data from this study indicate (1) the termination zone for VT susceptible to single capture termination almost always begins at the end of the effective refractory period; (2) the refractory period averages 11 ms longer with trains than with programmed stimulation, implying an effect of stimulation delivered during the refractory period; (3) programmed stimulation and ultrarapid train stimulation are equally effective in terminating VT; and (4) trains are more efficient than programmed stimulation for termination of a susceptible VT, because the arrhythmia will usually be terminated with the first capture and because the effectiveness of given train parameters is not altered by changes in the timing or duration of the termination zone.

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Cardiac Bioprostheses

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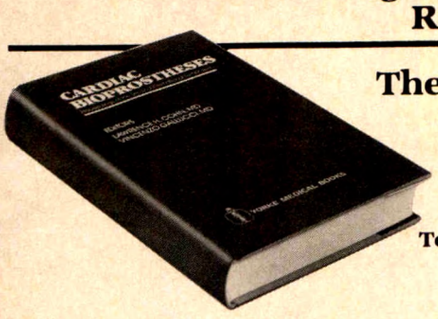

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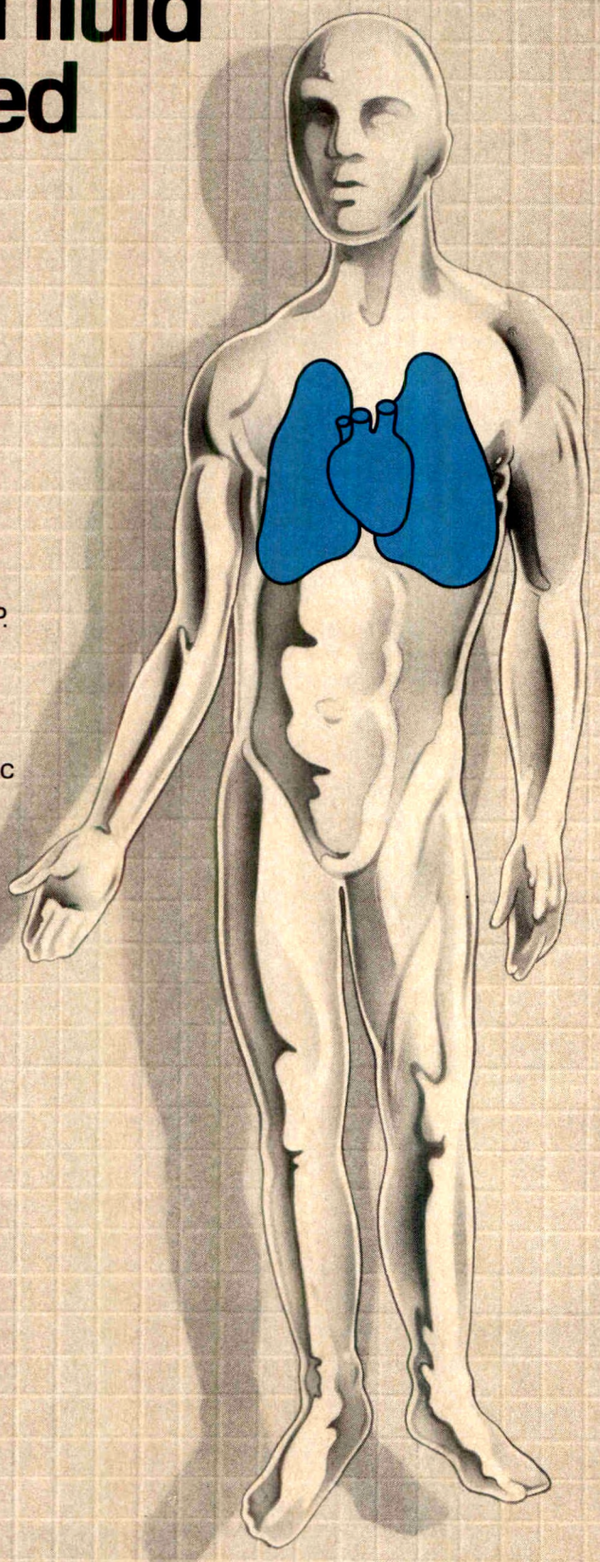
Therapeutic challenge:

Redistribution of fluid in CHF associated with acute MI



In Early CHF[1]

Pulmonary congestion with increased preload.

Findings: Elevated preload, elevated blood pressure, normal or slightly decreased cardiac output, PCWP greater than or equal to 18 mm Hg.

Therapeutic goal:
Reduce pulmonary congestion, lower PCWP to 15 to 18 mm Hg.

In Late CHF[1]

Pulmonary congestion with increased preload and afterload.

Findings: Low cardiac output, depressed blood pressure, and high PCWP.

Therapeutic goal:
Reduce pulmonary congestion, preload, and afterload, increase cardiac output, and lower PCWP to 15 to 18 mm Hg.

Why wait for the patient to become unresponsive to traditional diuretic/digitalis therapy?

1. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356-1362, 1404-1413.

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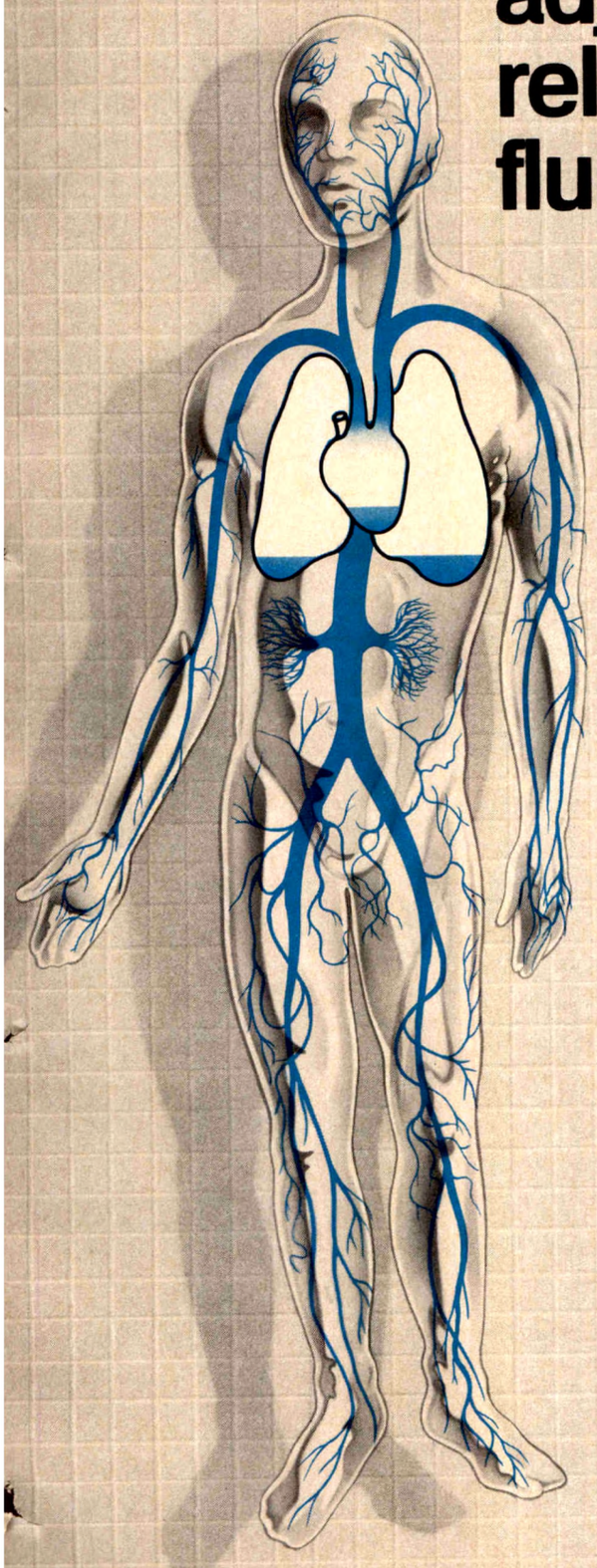
Give Tridil® (nitroglycerin) adjunctively to help relieve the fluid-burdened heart



In a dose-related manner, Tridil produces dilation of both arterial and venous beds—for a therapeutic redistribution of fluid.

Suggested therapy in early CHF

If blood pressure is normal:
Tridil to reduce preload and PCWP. Diuretics to decrease fluid volume.

If blood pressure is elevated:
Tridil should be initiated immediately to decrease preload, PCWP, and blood pressure, while maintaining coronary perfusion.

Suggested therapy in late CHF

If blood pressure is normal or only moderately depressed:
Vasopressors and Tridil adjunctively, with continuous hemodynamic monitoring.

If blood pressure is significantly depressed:
Vasopressors and Tridil adjunctively to reduce preload, afterload, and PCWP. Dopamine to increase the contractility of the myocardium. PCWP should be monitored.

Use of nonabsorbing Tridilset®

Sorptive loss of Tridil may range up to 80% when infused through a conventional PVC administration set[2] To overcome this problem, administer Tridil through Tridilset administration set or Tridilset V.I.P.™ volumetric pump connector set.

The most frequent adverse reaction in patients treated with Tridil is headache. Please see the following page for a brief summary of prescribing information. Note: Tridil is a potent drug and must be diluted before infusion.

For additional information, contact the Medical Services Department, American Critical Care, division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

2. Baaske DM, et al: Administration set suitable for use with intravenous nitroglycerin. *Am J Hosp Pharm* 1982;39:121-122.

TRIDIL® (nitroglycerin) SYSTEM

American Critical Care

TRIDIL® (nitroglycerin)

Brief Summary of Full Prescribing Information

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,® an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION

TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED

NDC 0094-0090-05, 25 mg-5 ml ampul. NDC 0094-0090-10, 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

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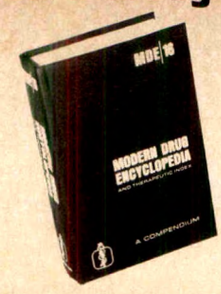

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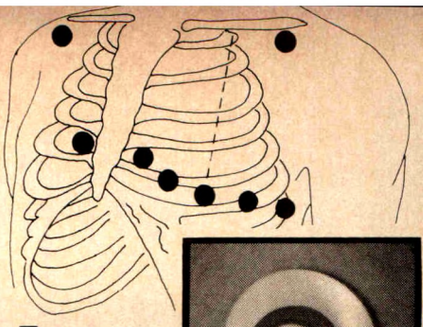

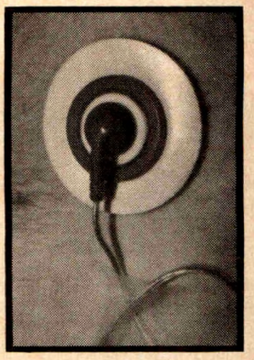

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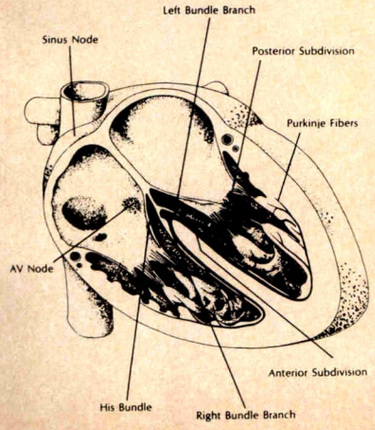

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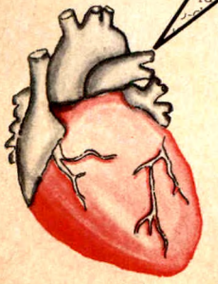

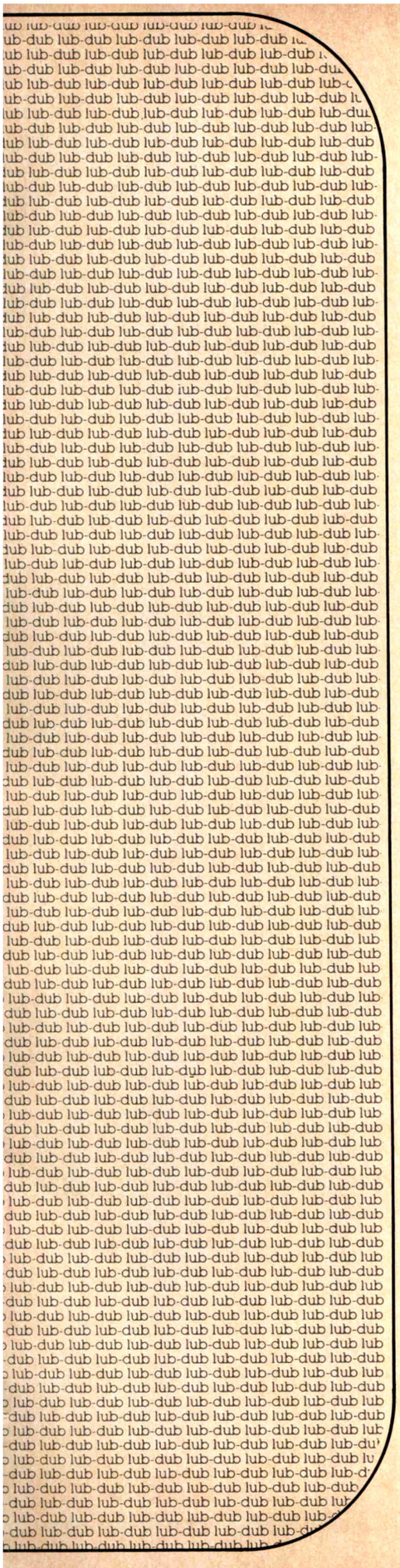

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Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs for overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, 'dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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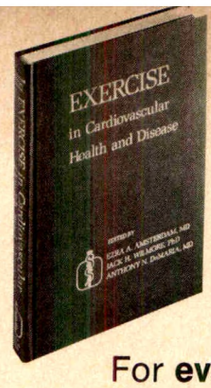

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Hemodynamic and Myocardial Performance Characteristics After Verapamil Use in Congestive Heart Failure

JACK FERLINZ, MD and P. DENNIS CITRON, MD

Because of its intrinsic negative inotropic effect, the administration of the recently introduced calcium antagonist, verapamil, is thought to be contraindicated in presence of congestive heart failure (CHF). Yet, as CHF is frequently associated with arrhythmias and angina pectoris, and verapamil possesses potent antiarrhythmic and antianginal properties that could be of great benefit to selected patients with CHF, this study was undertaken to determine whether verapamil can be given to such subjects safely. For this purpose, 14 patients with CHF were studied in the control (preverapamil) state with a combined hemodynamic-cineangiographic approach; the same interventions were repeated during intravenous verapamil administration (0.1 mg/kg bolus, followed by 0.005 mg/kg/min infusion). Verapamil markedly lowered mean aortic pressure (95 ± 19 to 81 ± 12 mm Hg, $p < 0.001$) and systemic vascular resistance (1,953 ± 873 to 1,417 ± 454 dynes s cm^{-5}, $p < 0.01$). Simultaneously, indexes of left ventricular (LV) performance substantially improved: the ejection fraction increased from 29 ± 13 to 37 ± 17% ($p < 0.01$), and mean velocity of circumferential fiber shortening increased from 0.45 ± 0.18 to 0.64 ± 0.28 circ/s ($p < 0.001$). Cardiac index also increased (from 1.98 ± 0.49 liters/m^2/min before verapamil to 2.24 ± 0.60 liters/m^2/min after verapamil), although this improvement did not become statistically significant. No appreciable changes were noted in the heart rate, LV end-diastolic pressure, or mean pulmonary arterial or pulmonary capillary wedge pressure. Thus, the intrinsic negative inotropic activity of intravenous verapamil in therapeutic doses generally does not represent a serious drawback even in patients with CHF; its potent unloading vasodilatory properties more than compensate for any intrinsic decrease in LV contractility, and can thereby actually improve overall cardiac function.

Calcium antagonists represent one of the most promising advances in cardiovascular pharmacology within the last decade. Their clinical usefulness was initially thought to be greatly limited, however, because of the vast array of presumed contraindications for their use. It was believed, for instance, that verapamil should be used only with great caution (if at all) in patients with coronary artery disease because both verapamil[1,2] and ischemia[3,4] interfere with the movement of calcium ions to the contractile proteins of the myocardial cells, and could in theory synergistically impede calcium transport, causing a profound depression of myocardial contractility. Recent studies in our laboratory[5,6] have shown that these fears were not justified, that verapamil can actually improve left ventricular (LV) function of patients with coronary heart disease, and that this effect can be documented not only in subjects with normal LV function, but also in patients with substantial LV asynergy.[7,8] It is still maintained, however, that verapamil should not be given to patients with congestive heart failure (CHF) because, under these circumstances, the intrinsic negative inotropic effect of verapamil may not only exacerbate CHF, but could conceivably even lead to fatal complications. To the extent that arrhythmias are exceedingly common (and angina pectoris fairly frequent) in patients with CHF, and verapamil is probably the drug of choice for many, the usefulness of the drug would be severely curtailed if the presence of CHF indeed represented an absolute contraindication to its administration. This study was therefore undertaken to characterize in detail verapamil's effects

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Address for reprints: Jack Ferlinz, MD, Chairman, Division of Adult Cardiology, Cook County Hospital, 1835 West Harrison Street, Chicago, Illinois 60612.

TABLE I Clinical Profile of the Patient Population

Patients (n)	14
Age (years)*	57 ± 6
Cardiac pathology	
Cardiomypathy	2 (14%)
Coronary artery disease (CAD)	5 (36%)
Cardiomyopathy + CAD	7 (50%)
New York Heart Association classification	
Class III	6 (43%)
Class IV	8 (57%)
Cardiothoracic ratio (chest x-ray)*	0.56 ± 0.05
LV MAS (M-mode echo)*	19 ± 7%
LV EF (radioisotope)*	29 ± 14%
History of CHF	All

* Mean ± 1 standard deviation.
CHF = congestive heart failure; EF = ejection fraction; LV = left ventricular; MAS = minor axis shortening.

on the cardiovascular system of patients with CHF, and to establish whether intravenous verapamil can be given to such subjects safely despite previous caveats.

Methods

Fourteen consecutive patients with clinical, roentgenographic, and hemodynamic features of CHF who needed cardiac catheterization for purely diagnostic purposes were selected for this study. A clinical profile for the entire patient population is presented in Table I. All gave informed consent and underwent routine diagnostic cardiac catheterization studies, which, in our laboratory, include complete left and right heart hemodynamic evaluation, cardiac output determination with the indocyanine green indicator-dilution technique, selective left ventriculography, and coronary arteriography. All patients were in normal sinus rhythm; none had significant valvular or congenital lesions. Patients with clinically significant renal or hepatic failure, left bundle branch block, sinus bradycardia, systolic blood pressure <90 mm Hg, or recent myocardial infarction were excluded from the study. No patient had to be excluded from the study because of adverse effects caused by verapamil, or because complete hemodynamic and volumetric evaluation could not be performed for clinical or technical reasons.

All patients were receiving other cardiovascular medications, but in each instance all drugs except sublingual nitroglycerin were discontinued at least 3 days before the study. All patients were carefully monitored throughout the drug wash-out period for any untoward effects related to the temporary cessation of their medications. Some patients had mild to moderate increases in their symptoms (mostly shortness of breath), but there was no obvious clinical evidence for further deterioration of their cardiac function which would mandate the resumption of prior medical therapy before the study could be initiated. Most subjects (13) were receiving digitalis preparations before the study; the digoxin plasma drug level was <0.50 ng/ml (the limit of our laboratory's ability to determine the presence of the drug) at the time of the study in every single case. No patient had to take nitroglycerin for at least 10 hours before cardiac catheterization.

After the first ventriculogram and coronary arteriography, 0.1 mg/kg of verapamil was given as a bolus intravenously over a 2-minute period; the intravenous verapamil infusion of 0.005 mg/kg/min was started with a Harvard infusion pump immediately after the bolus injection and continued until all data were collected. The mean bolus dose of verapamil was 7.8 ± 1.4 mg; the infusion dose 7.4 ± 3.1 mg, and the total dose 15.3 ± 4.4 mg; the length of the infusion averaged 18 ± 4 minutes. Forty-five minutes after the first ventriculography (and 15 minutes after coronary angiography), the second left ventriculogram was performed during verapamil infusion. Forty-five minutes were allowed to elapse between first and second ventriculograms to eliminate the pharmacologic effects of the contrast medium on myocardial contractility,[9] and 15 minutes elapsed after the coronary cineangiography in order to avoid the possible effects of transient reactive hyperemia on myocardial contractility.[10]

TABLE II Cardiovascular Changes Induced by Verapamil Administration

Variable	Before Verapamil (Mean ± SD)	After Verapamil (Mean ± SD)	Significance (p)
Systolic AP (mm Hg)	125 ± 24	109 ± 19	<0.001
Diastolic AP (mm Hg)	74 ± 15	65 ± 9	<0.01
Mean AP (mm Hg)	95 ± 19	81 ± 12	<0.001
Mean RAP (mm Hg)	7 ± 4	10 ± 5	<0.001
Mean PAP (mm Hg)	33 ± 15	32 ± 12	NS
Mean PCWP (mm Hg)	20 ± 9	19 ± 8	NS
SVR (dynes s cm^{-5})	1,953 ± 873	1,417 ± 454	<0.01
PVR (dynes s cm^{-5})	303 ± 234	267 ± 171	NS
LVEDP (mm Hg)	25 ± 7	24 ± 9	NS
RVEDP (mm Hg)	10 ± 4	13 ± 5	<0.01
$(A\text{-}V)O_2$ (vol %)	6.7 ± 2.2	5.7 ± 1.8	<0.05
CI (liters/min/m^2)	1.98 ± 0.49	2.24 ± 0.60	NS
HR at CI (beats/min)	81 ± 14	81 ± 10	NS
HR at V-gram (beats/min)	85 ± 15	82 ± 10	NS
EDVI (ml/m^2)	202 ± 77	215 ± 77	NS
ESVI (ml/m^2)	147 ± 68	118 ± 60	NS
SVI (ml/m^2)	55 ± 21	75 ± 30	<0.01
EF (%)	29 ± 13	37 ± 17	<0.01
V_{CF} (circ/s)	0.45 ± 0.18	0.64 ± 0.28	<0.001
E_{cc} (diastolic)	0.70 ± 0.10	0.69 ± 0.12	NS
E_{cc} (systolic)	0.76 ± 0.08	0.76 ± 0.11	NS

AP = arterial pressure; $(A\text{-}V)O_2$ = arteriovenous difference; CI = cardiac index; Ecc = eccentricity; EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; NS = not significant; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; SD = standard deviation; SVI = stroke volume index; SVR = systemic vascular resistance; V-gram = cineangiographic ventriculogram; Vcf = mean velocity of circumferential fiber shortening.

Both selective left ventriculograms were obtained with a No. 8 Cordis pigtail catheter positioned in the left ventricle. Forty-five to 50 ml of 76% meglumine sodium diatrizoate (Renografin®-76) was injected over a 3-second interval. Left ventriculograms in 30° right anterior oblique position were recorded at 64 frames/s on 35 mm Ilford Cinegram F film with a Philips 9-inch image intensifier. Two independent observers analyzed only the first 4 beats after complete opacification. If an infrequent premature ventricular contraction was detected, at least 2 successive normal sinus beats (after the premature beat) had to occur before a frame was selected for analysis.

A modification[11] of the area-length method of Dodge[12] was used in the analysis of all LV volumes. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), and ejection fraction (EF = SVI/EDVI) were calculated for each patient.

Each ventriculogram was interpreted qualitatively for vigor and uniformity of contractions at all points along the LV outline. A quantitative analysis was performed by combining previously described approaches[13,14] and using internal thoracic structures (spine, rib margins, or a diaphragm) as fixed references. End-systolic (ES) and end-diastolic (ED) images were fitted with a longitudinal axis (obtained by dividing the

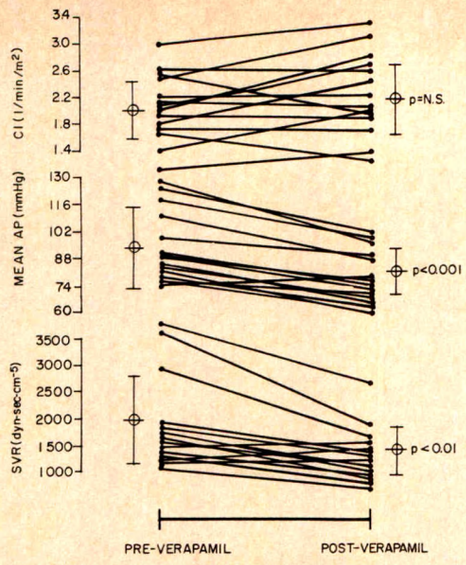

FIGURE 1. Changes in cardiac index (CI), mean arterial pressure (AP), and systemic vascular resistance (SVR) with verapamil therapy. N.S. = not significant.

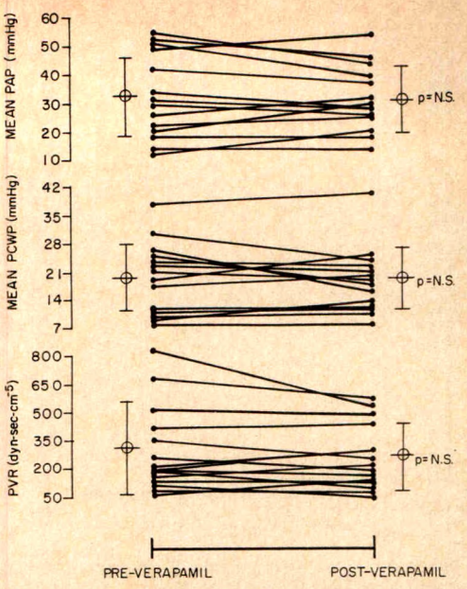

FIGURE 2. Effects of verapamil on right-sided pressures (mean pulmonary artery [PAP] and mean pulmonary capillary wedge [PCWP]) and pulmonary vascular resistance (PVR). N.S. = not significant.

images with a connecting line between the bisected aortic valve and the ventricular apex) and 6 hemiaxes (perpendicular to the longitudinal axis, which was divided into 4 equal segments). The longitudinal axis and each hemiaxis were then measured and normalized as percent decrease (or increase) in length from the ED dimension: Percent shortening = [(ED axis − ES axis)/ED axis] ×100.

A hypokinetic zone was defined when <25% hemiaxis shortening was observed in the initial ventriculogram.[15] According to the classification of Herman et al,[16] hypokinesia represented the mildest form of asynergy, followed by increasingly more pronounced LV wall-motion abnormalities when akinesia and dyskinesia were encountered. An increase in shortening ≥10% after administration of verapamil was considered an improvement in an asynergic segment,[15] and a decrease ≥10% a deterioration.

Cardiac output (CO), arterial-venous difference, and pressure data were collected just before each ventriculogram. CO was determined with the Lyons indocyanine green indicator-dilution computer by averaging 4 sequential measurements. All pressures—aortic (AP) and pulmonary artery (PAP) systolic, diastolic, and mean; right and left ventricular systolic and end-diastolic; mean right atrial (RAP); and mean pulmonary capillary wedge (PCWP)—were measured with Statham model P23Db strain gauges and recorded with an Electronics for Medicine VR-16 recorder over 3 full respiratory cycles. Systemic pressure was recorded 1, 3, 5, 10, and 15 minutes after the verapamil bolus was administered. Blood samples were drawn for serum verapamil level determination at the same time intervals, and assayed with high-pressure liquid chromatography[17] in the Bio-Science Laboratories. Heart rate was monitored throughout the study. In addition, systemic vascular resistance (SVR = [mean AP − mean RAP]/CO), pulmonary vascular resistance (PVR = [mean PAP − mean PCWP]/CO), and mean velocity of circumferential fiber shortening (Vcf = [^{d}ED − ^{d}ES]/[^{d}ED × ejection time], where ^{d}ED and ^{d}ES are left ventricular minor axes in end-diastole and end-systole),[18] were calculated for each patient.

Because it was anticipated that the LV geometry of these subjects with CHF will be substantially distorted, the LV eccentricity (E_{cc})[19] or "globularity"[20] was also determined in end-systole and end-diastole by using the expression: $E_{cc} = \sqrt{(\frac{1}{2}\,l)^2 - (\frac{1}{2}\,d)^2}/\frac{1}{2}\,l$, where l is the directly measured longitudinal axis and d the calculated minor axis (d = [4 × LV area]/[π × l]). In this schema, E_{cc} varies from 0 to 1, a perfect sphere having the E_{cc} of zero. A failed, dilated, spherical ventricle will, therefore, have a lower E_{cc} than a normal, elongated, ellipsoid one. Furthermore, the normal change in LV geometry from a more globular shape at end-diastole to a more elongated configuration at end-systole is usually attenuated in failing hearts.

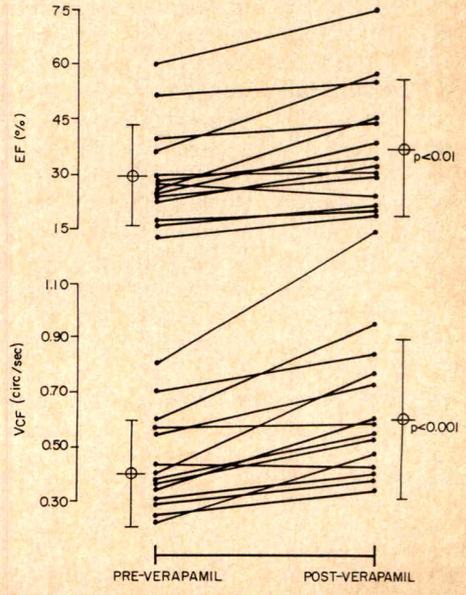

FIGURE 3. Verapamil's influence on indexes of myocardial performance (ejection fraction [EF] and mean velocity of circumferential fiber shortening [VCF]).

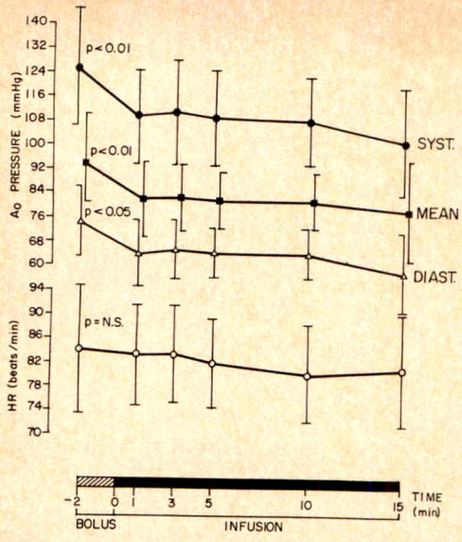

FIGURE 4. Effects of verapamil on aortic (Ao) pressures and heart rate (HR) after bolus and during infusion. (P values denote the significance of verapamil-induced changes in comparison with the control state.) DIAST. = diastolic; SYST. = systolic.

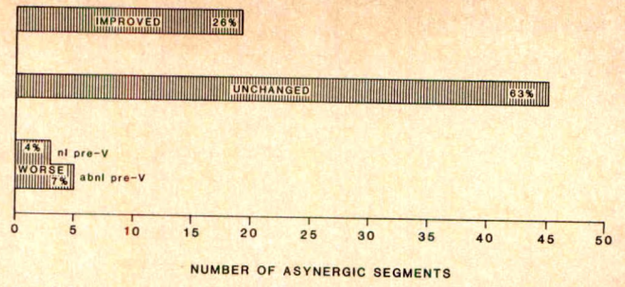

FIGURE 5. Changes in left ventricular contractility after administration of verapamil (V). abnl = abnormal; nl = normal.

All coronary cineangiograms were of high technical quality. Significant coronary artery disease was considered present only when there was at least a 75% diameter occlusion of at least 1 of the 3 coronary arteries, and when this observation was confirmed by 2 independent observers.

All data were analyzed with the 2-tailed t test for paired variables.

Results

The complete mean hemodynamic and volumetric data obtained before and after verapamil administration for the entire group are given in Table II, and a summary of key cardiovascular findings for each patient in Figures 1, 2, and 3. Verapamil markedly lowered aortic pressure and systemic vascular resistance. The decrease in systolic, mean, and diastolic aortic pressure occurred almost immediately after bolus administration, and was then effectively maintained with only very minor fluctuations at this lower level throughout the duration of the infusion (Fig. 4). While the decrease in aortic pressure from control values was highly significant, none of the minor variations that occurred after the verapamil infusion was started were statistically significant when compared with each other. Heart rate, however, remained essentially unchanged when values before and after verapamil administration were compared (Fig. 4). Specifically, heart rates recorded during CO measurements and ventricular cineangiography were virtually identical before and after administration of verapamil and could not, therefore, influence the observed results.

Verapamil caused a significant increase in the right atrial and right ventricular end-diastolic pressure, but there was actually a slight decrease in the mean PAP, PCWP, and PVR, and the LV end-diastolic pressure (LVEDP). Arterial-venous difference [(A-V)O_2] and CO were both substantially improved, achieving a statistical significance for the former but not for the latter. Volumetric analysis revealed that LV end-diastolic volume does not change after verapamil administration. End-systolic volume decreases, however, causing a significant increase in stroke volume, ejection fraction, and velocity of circumferential fiber shortening (Vcf).

Verapamil did not cause a further distortion of LV geometry in that LV E_{cc} did not change during verapamil infusion. Furthermore, while all patients had regional disorders of LV contractility (delineated by abnormal shortening of 72 hemiaxes) after administration of verapamil, 19 of 72 asynergic segments improved (26%), 45 remained unchanged (63%), and 5 worsened (7%). In addition, 3 previously normal segments (4%) became asynergic after verapamil. Overall, however, 89% of all asynergic (or potentially asynergic) segments improved or remained the same after the drug was administered, while only 11% deteriorated further (Fig. 5).

Serum verapamil level assay became available to us when the last patient was enrolled in the study. Figure 6 depicts the blood levels obtained in this subject during the bolus and the infusion parts of the experiment. Very high initial serum verapamil levels were registered after the bolus administration; the blood levels then stabilized between 100 and 200 ng/ml during verapamil infusion. (In a recent study investigating the effects of intravenous verapamil on the hemodynamic status of patients with coronary artery disease, similar blood levels have been shown to produce a substantial circulatory response.[21]) Concomitantly with the increase in the serum verapamil concentration, a large decrease in the mean aortic pressure and a moderate decrease in the heart rate were also observed (Fig. 6). Hemodynamic and volumetric variables collected in the same patient after a steady-state serum verapamil concentration was reached are depicted in Figure 7. A beneficial response in all measured variables with verapamil is unmistakable.

Discussion

The earlier concepts which have maintained that administration of verapamil produces profound negative inotropic effects even in normal hearts[22–24] have been largely abandoned in view of the extensive recent evidence demonstrating that verapamil acts more as an

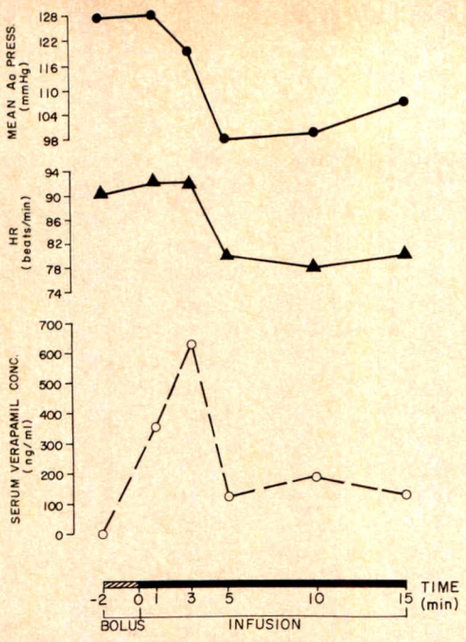

FIGURE 6. Serum verapamil blood levels and concomitant changes in mean aortic (Ao) pressure and heart rate (HR) after bolus and during infusion. CONC. = concentration; PRESS. = pressure.

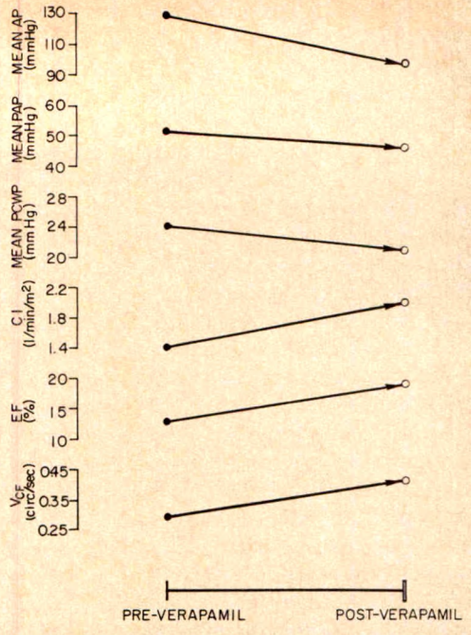

FIGURE 7. Beneficial response in all measured variables (mean arterial pressure [AP], mean pulmonary artery pressure [PAP], mean pulmonary capillary wedge pressure [PCWP], cardiac index [CI], ejection fraction [EF], and mean velocity of circumferential fiber shortening [V_{cf}]) of the patient whose verapamil blood levels are depicted in Figure 6.

unloading agent than a myocardial depressant.[5,6,25–28] It is still widely believed, however, that verapamil should be given with the greatest caution (if at all) to patients who have a significant impairment of LV function, and that subjects with severe CHF should be excluded altogether.[29–31] Yet, because patients with CHF routinely have concomitant cardiac conditions (such as arrhythmias and angina) that are ideally suited for verapamil therapy, a very large number of candidates for verapamil treatment are denied the benefit of this drug because of such caveats.

Preliminary reports have already indicated that some investigators do not find CHF an absolute contraindication to verapamil use,[8,32,33] especially when CHF occurs in the setting of supraventricular tachycardia.[32,33] It remains to be seen, however, what actual hemodynamic changes take place when intravenous verapamil is administered to patients with *severe* CHF who are in normal sinus rhythm, and the extent (if any) of subsequent LV deterioration.

Previous experiments with a different calcium antagonist which does not possess antiarrhythmic properties—nifedipine—have demonstrated that this drug can not only be given safely to patients with CHF,[34–38] but that it can actually be used to treat pulmonary edema.[39] This approach was purportedly not to be used with verapamil, however, because verapamil was not the vasodilator of nearly the same potency as nifedipine,[29,40–42] and its negative inotropic effects would exert themselves at a substantially lower unloading plateau than nifedipine's.[43–45]

These premises were not substantiated in our study. Ejection fraction and Vcf increased in all but 1 patient with verapamil treatment, and even in this subject the decrease was only slight. Furthermore, LV E_{cc}, while obviously already abnormal in the control phase of the study, did not worsen during verapamil administration. (Normal LV E_{cc} varies from 0.85 ± 0.01 in end-diastole to 0.92 ± 0.01 in end-systole; in severely decompensated hearts LV E_{cc} decreases to 0.70 ± 0.01 in end-diastole and 0.73 ± 0.01 in end-systole.[20]) Finally, we found no evidence that verapamil will exacerbate LV asynergy in patients with CHF, since 89% of all asynergic segments improved or remained the same after the drug was administered, and only 11% deteriorated further. In 2 patients spontaneous pulmonary edema developed in the cardiac catheterization laboratory during the control phase of the study, before any amount of verapamil was administered. Verapamil was then given to them in the quantities mandated by the protocol not only because it was considered safe to complete the experiment, but also to ascertain whether pulmonary edema can be ameliorated by verapamil. Both patients' conditions improved.

It is apparent that the major beneficial attribute of verapamil promulgating the improvement in the LV function of our CHF patients is its ability to induce potent peripheral vasodilatation. Verapamil produced a highly significant drop in the aortic pressure and systemic vascular resistance, thereby greatly reducing the impedance to ventricular ejection. Additional beneficial effect may be due to the drug's propensity to improve the myocardial diastolic relaxation that is often severely impaired in compromised hearts.[46–48] It is rather doubtful, however, that verapamil's potent in vitro coronary vasodilating action could exert itself in

actual patients and therefore contribute to the improvement in ventricular function through the augmented myocardial blood supply: experiments in our laboratory have shown that verapamil administration (by decreasing myocardial metabolic demands) may actually decrease the coronary flow when given to the subjects with ischemic heart disease.[49–52]

It has been well established that verapamil tends to increase right-sided pressures, PCWP, and LVEDP of patients with essentially normal hearts.[5–8,53,54] Of interest, therefore, is the finding that the patients in this study did not have increases in PAP, PCWP, or LVEDP. It is tempting to speculate that if, indeed, the normal effect of verapamil in the non-CHF patients is to augment the right heart and LV filling pressures, the potent vasodilatory properties of the drug would actually decrease these pressures in the CHF subjects (as other vasodilators commonly do) if it were not for verapamil's propensity to act otherwise. It is, therefore, possible that verapamil's failure to actually decrease the LV filling pressure in the CHF patients represents the net result of these 2 opposing modalities of action.

A number of vasodilators have been used with a fair amount of success in the treatment of CHF.[55–58] Yet, recent evidence indicates that vasodilator therapy for CHF can sometimes produce profound adverse effects.[59,60] Specifically, administration of hydralazine[61] or nifedipine[62] can trigger increased frequency of anginal attacks; with hydralazine these ischemic events sometimes lead to myocardial infarction or even death.[61] To the extent that 12 of 14 CHF patients (86%) in our study also had concomitant coronary artery disease, it was important to assess verapamil's potential to provoke similar ischemic episodes. They were not detected in any of the subjects.

Despite the encouraging nature of data presented in this study, however, it should not be assumed that verapamil is incapable of producing serious adverse effects. In this context, under no circumstances should this communication be interpreted as endorsing intravenous verapamil for the treatment of congestive heart failure, or even pulmonary edema. As already stated, 1 of our patients experienced a slight decrease in ejection fraction and Vcf; his PCWP and LVEDP concomitantly increased—albeit only a little, and his cardiac output and E_{cc} registered a modest decrease. It is conceivable that this subject came close to a total cardiovascular decompensation, and that this putative decompensation would have been mostly verapamil-related. Nevertheless, in the doses administered in this study, verapamil did not produce any overt untoward effects, and was most often hemodynamically outright beneficial.

That the dose employed is of critical importance deserves a special emphasis. Chew et al[30] have reported that a subset of 3 patients with markedly reduced LV ejection fraction and elevated mean PCWP, mean arterial pressure decreased substantially with a concomitant decrease in stroke volume index and an abrupt further increase in mean PCWP after verapamil administration. The bolus dose of verapamil used (0.145 mg/kg), however, was subtantially higher than in our study. Verapamil's negative inotropic effect becomes even more prominent at very high doses, and it eventually leads to a profound depression of myocardial contractility when such quantities of the drug are employed.[63] In the precariously functioning hearts of patients with CHF, the beneficial unloading effects of verapamil will probably be overcome fairly readily by the drug's negative inotropic effect if very large quantities of this drug are given.

This dose-dependent relation will become especially important if *oral* verapamil is to be given to patients in CHF. Epstein and Rosing[64] report serious hemodynamic complications and even deaths with use of oral verapamil in treatment of patients with hypertrophic cardiomyopathy. One of their patients with serious complications (hypotension, pulmonary edema) had an excessively high blood level of the drug. Such an overshoot can probably occur fairly readily because of the enormous interpatient variations in their first-pass metabolism of oral verapamil. In a recent study with the oral preparation, patients received a maintenance dose of 480 mg of verapamil per day, and then challenged with an additional 160 mg test dose.[65] A *25-fold* difference between patients taking this dosage was found for verapamil plasma concentrations before the test dose and a 13-fold difference after it. The concentration of the main active verapamil metabolite, norverapamil, showed a strong positive correlation with the corresponding verapamil concentrations. The problems with the unpredictable bioavailability of oral verapamil (at least as assessed by verapamil plasma concentration) are further compounded by the drug's long-term effect on the reflex adrenergic response. It has been reported that catecholamine levels are elevated when verapamil is given on a short-term basis, suggesting a decrease in peripheral resistance and reflexly increased sympathetic activity.[66] In a long run, however, these reflex-mediated responses dissipate, and CHF may develop or worsen when catecholamine levels return to control levels.

The findings from this short-term intravenous study must, therefore, not be extrapolated to the long-term action of oral verapamil in CHF. A need for a long-term evaluation of the oral preparation of this drug in CHF is pressing, and we have therefore started the consenting patients from this study on a verapamil maintenance therapy in an attempt to also elucidate its long-range cardiovascular effects.

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Efficacy of Prazosin in the Management of Chronic Congestive Heart Failure: A 6-Month Randomized, Double-Blind, Placebo-Controlled Study

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The beneficial effects of acute prazosin therapy in patients with congestive heart failure (CHF) have been well documented; however, its chronic efficacy over several months has not previously been evaluated in a placebo-controlled manner. Therefore, an assessment was made by radionuclide ventriculography of the effect of prazosin, 20 mg/day, on left ventricular ejection fraction and end-systolic and end-diastolic volumes at rest and on peak upright bicycle exercise, as well as its effect on right ventricular ejection fraction at rest, exercise time and work load, and standard clinical variables in 23 patients with stable class III symptoms of CHF. The study consisted of a 6-month randomized, double-blind, controlled evaluation of prazosin versus placebo in patients receiving a stable dose of digitalis and diuretics for at least 1 month. At entry, the prazosin and placebo groups did not differ in any respect. Prazosin caused no demonstrable effect on clinical variables such as status of symptoms, heart rate, mean arterial pressure, and cardiothoracic ratio when compared with placebo. Prazosin also caused no demonstrable effect compared with placebo on absolute or percent changes in radionuclide variables at rest or on peak exercise, or on exercise time or exercise work load. In addition, prazosin had no consistent effect compared with placebo on plasma renin activity or plasma catecholamine levels. However, there was a slight but significant increase in weight ($p < 0.0001$) and in plasma renin activity in the upright position ($p < 0.002$) with time, as well as a tendency for the diuretic dose to increase with time in both groups. Thus, long-term prazosin therapy generally produces no demonstrable subjective or objective improvement in patients with stable, chronic class III CHF receiving digitalis and diuretic therapy.

Vasodilator therapy of congestive heart failure (CHF) represents an attractive conceptual alternative or adjunct to inotropic support of the failing heart. Prazosin, an orally active postsynaptic alpha-adrenergic antagonist,[1] has been shown to produce a balanced effect on both the venous and arterial systems, with a resultant increase in cardiac output and decrease in pulmonary congestion, in short-term studies in patients with CHF.[2–4] However, its long-term efficacy is in dispute. Tolerance appears to be a common problem,[5–9] and may be related to an increase in plasma norepinephrine levels[10,11] or plasma renin activity.[12,13] In order to further elucidate this problem, we performed a 6-month, randomized, double-blind, placebo-controlled study of the effects of prazosin in patients with New York Heart Association (NYHA) class III CHF. We assessed exercise capacity, left ventricular function at rest and during peak exercise, right ventricular function at rest, plasma renin and catecholamine levels, and standard clinical variables at several discrete points in time during the study.

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Methods

Patients: The study population comprised 25 patients (14 men and 11 women, aged 30 to 76 years) with chronic CHF. Thirteen (8 men and 5 women) were randomized to prazosin and 12 (6 men and 6 women) to placebo groups. All had pre-

died suddenly. Other than hypotension in 1 patient, prazosin was tolerated well by all patients.

Clinical variables: There was no significant improvement in NYHA class attributable to prazosin at any time period (Fig. 1). There was an increase in body weight with time ($p < 0.0001$) in both groups of patients (prazosin group: at baseline 72 ± 17 kg, at 26 weeks 74 ± 18 kg; placebo group: at baseline 74 ± 17 kg, at 26 weeks 78 ± 15 kg) (Fig. 1). The difference between the groups was not significant. There was also an increase in furosemide dosage with time in both groups that did not attain the designated level of statistical significance (Fig. 1). Mean arterial pressure and heart rate, both sitting and standing, were not different at any time between the groups and did not change significantly with time. (Only the standing mean arterial pressure data are presented in Figure 1). Cardiothoracic ratio also showed no significant change with time or in response to prazosin therapy at any time period (prazosin group: at baseline 56 ± 8%, at 12 weeks 53 ± 10%, at 26 weeks 55 ± 10%; placebo group: at baseline 56 ± 7%, at 12 weeks 56 ± 8%, at 26 weeks 53 ± 9%).

Radionuclide variables: Prazosin did not produce an improvement compared with placebo in any of the radionuclide variables (Tables II and III). At rest, the left ventricular ejection fraction increased slightly, but not significantly, with time in both groups (prazosin group: 0.25 ± 0.09 at baseline, 0.27 ± 0.09 at 4 weeks, 0.30 ± 0.08 at 26 weeks; placebo group: 0.21 ± 0.08 at baseline, 0.23 ± 0.08 at 4 weeks, 0.25 ± 0.13 at 26 weeks). At peak exercise, left ventricular ejection fraction increased with time in both groups ($p < 0.004$). The difference between the groups was not significant at any time period (prazosin group: 0.24 ± 0.05 at baseline, 0.30 ± 0.08 at 4 weeks, 0.31 ± 0.10 at 26 weeks; placebo group: 0.24 ± 0.10 at baseline, 0.25 ± 0.10 at 4 weeks, 0.28 ± 0.12 at 26 weeks). There was also no clearly discernible improvement in individual patients in either of these variables in response to prazosin therapy (Figs. 2 and 3). At rest, end-diastolic and end-systolic volume indexes in the prazosin group were 151 ± 70 and 113 ± 52 ml/m^2, respectively, at baseline and did not change significantly with time. Similarly, end-diastolic and end-systolic volume indexes at baseline in the placebo group were 155 ± 62 and 125 ± 57 ml/m^2 and did not change significantly with time. At peak exercise, end-diastolic and end-systolic volume indexes also did not change significantly with time or with prazosin therapy. The right ventricular ejection fraction at baseline averaged 0.42 ± 0.19 in the prazosin group and 0.41 ± 0.18 in the placebo group and showed no significant change with time or in response to prazosin therapy. Neither the absolute nor the percent change in any of these radionuclide variables suggested a beneficial effect from prazosin therapy at any time period.

TABLE II Radionuclide and Exercise Variables (Prazosin Group)

	4 Weeks	12 Weeks	26 Weeks
Peak work load (kpm/min)	235 ± 163	261 ± 158	278 ± 169
Exercise duration (s)	540 ± 156	519 ± 150	539 ± 186
Percent maximum predicted HR	76 ± 11	76 ± 15	76 ± 17
Resting LVEF	0.27 ± 0.09	...	0.30 ± 0.08
Ex LVEF	0.30 ± 0.08	...	0.31 ± 0.10
Resting LVEDVI (ml/m^2)	151 ± 55	...	162 ± 77
Ex LVEDVI (ml/m^2)	156 ± 62	...	167 ± 89
Resting LVESVI (ml/m^2)	112 ± 47	...	117 ± 61
Ex LVESVI (ml/m^2)	111 ± 47	...	114 ± 57
RVEF	0.43 ± 0.15	...	0.36 ± 0.19

Abbreviations as in Table I.
Eleven patients at 4 weeks, 9 patients at 12 weeks, 8 patients at 26 weeks. For RVEF, 10 patients at 4 weeks, 5 patients at 26 weeks.

TABLE III Radionuclide and Exercise Variables (Placebo Group)

	4 Weeks	12 Weeks	26 Weeks
Peak work load (kpm/min)	254 ± 88	255 ± 103	266 ± 114
Exercise duration (seconds)	546 ± 120	558 ± 196	581 ± 162
Percent maximum predicted HR	76 ± 15	74 ± 16	79 ± 17
Resting LVEF	0.23 ± 0.08	...	0.25 ± 0.13
Ex LVEF	0.25 ± 0.10	...	0.28 ± 0.12
Resting LVEDVI (ml/m^2)	142 ± 56	...	154 ± 68
Ex LVEDVI (ml/m^2)	150 ± 58	...	163 ± 63
Resting LVESVI (ml/m^2)	113 ± 50	...	121 ± 65
Ex LVESVI (ml/m^2)	116 ± 51	...	124 ± 55
RVEF	0.44 ± 0.16	...	0.54 ± 0.13

Abbreviations as in Table I.
Twelve patients at 4 weeks, 11 patients at 12 weeks, 8 patients at 26 weeks. For RVEF, 9 patients at 4 weeks, 5 patients at 26 weeks.

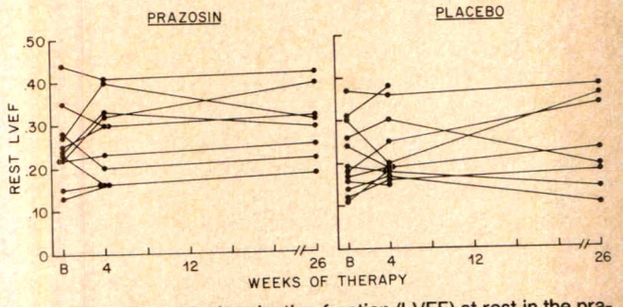

FIGURE 2. Left ventricular ejection fraction (LVEF) at rest in the prazosin- and placebo-treated patients. Each line represents the data from 1 patient. There was no significant difference in response between the 2 groups.

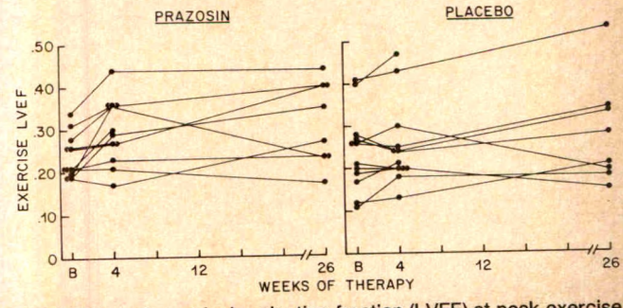

FIGURE 3. Left ventricular ejection fraction (LVEF) at peak exercise in the prazosin- and placebo-treated patients. Each line represents the data from 1 patient. There was no significant difference in response between the 2 groups.

Exercise variables: There was no significant increase with time in either total exercise duration (Fig. 4) or work load achieved (Tables I to III) in response to prazosin or placebo. Neither the absolute change nor the percent change in either of these exercise variables suggested an improvement in function in response to prazosin therapy at any time period.

Neurohumoral variables: The neurohumoral variables for each group at each time period are shown in Table IV. In the prazosin group, plasma norepinephrine levels increased in 8 of the 11 patients at 4 weeks and the mean value increased from 790 ± 280 pg/ml at baseline to 1,413 ± 1,030 pg/ml. However, this change was not significant, and at 26 weeks the plasma norepinephrine level at rest was 875 ± 638 pg/ml. Plasma norepinephrine levels at peak exercise tended to increase with time in both prazosin and placebo groups; however, this change again did not attain statistical significance. Plasma epinephrine levels showed no significant alterations with time or in response to prazosin therapy. Plasma renin activity also did not change significantly in response to prazosin therapy but increased with time, both in the standing ($p < 0.002$) and supine ($p = 0.015$) positions, in both groups.

Discussion

The beneficial effects of acute prazosin therapy in patients with CHF have been well documented.[2–4] Recently, 2 double-blind, randomized, placebo-controlled studies[12,24] demonstrated a beneficial effect from long-term prazosin therapy after 6 and 8 weeks, respectively, while a third double-blind, randomized, placebo-controlled, crossover study[25] demonstrated acute improvement in hemodynamic characteristics but marked attenuation of the hemodynamic effects after 4 weeks of prazosin therapy. The present study, which is the first double-blind, randomized, placebo-controlled study of chronic prazosin therapy in CHF that extends over several months with serial evaluations at several discrete points in time during the study demonstrated no beneficial effect at any time during this study, either at rest or during exercise.

Clinical variables: The patients randomized to prazosin and placebo were well matched in every respect (Table I). The average compliance (89% by pill count) over the total duration of the study was good. Prazosin had no demonstrable effect compared with placebo on clinical symptoms or signs at any time during the study. A consistent effect on heart rate or blood pressure, either sitting or standing, could not be demonstrated. There was also no significant change in cardiothoracic ratio as assessed by chest roentgenography at 3 or 6 months of therapy. There was a slight but significant ($p < 0.001$) increase in weight in both prazosin- and placebo-treated groups of patients with time despite a trend towards a concomitant increase in furosemide dosage. The increase in weight and furosemide dosage between the prazosin and placebo groups was not significantly different at any time. Prazosin was generally well tolerated. Only 1 patient had limiting postural hypotension and was excluded from the study after the first day of therapy.

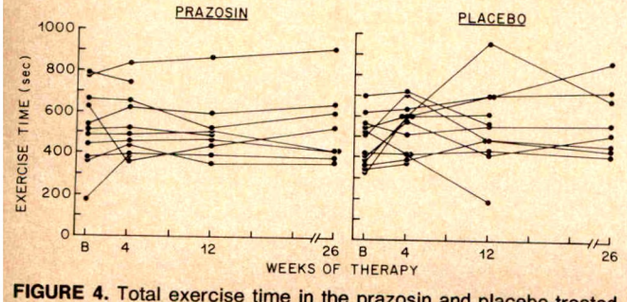

FIGURE 4. Total exercise time in the prazosin and placebo-treated patients. Each line represents the data from 1 patient. There was no significant difference in response between the 2 groups.

Radionuclide variables: Radionuclide-determined left ventricular ejection fraction, end-diastolic and end-systolic volume indexes, and right ventricular ejection fraction at rest showed no significant change in response to prazosin, either at 1 or 6 months. These findings contrast strikingly with those reported by Colucci et al who observed an increase in both left[12] and right[26] ventricular ejection fractions after 2 months of prazosin therapy. The left ventricular ejection fraction before therapy in the patients who received prazosin (0.25 ± 0.09) was similar to that reported in the study by Colucci et al[12] (0.25 ± 0.02), while the right ventricular ejection fraction was higher in our patients (0.42 ± 0.19 versus 0.28 ± 0.04). The other 2 double-blind studies of chronic prazosin therapy[24,25] did not report left ventricular ejection fractions or volumes and, therefore, cannot be compared directly with ours.

Several other investigators[27–29] have been unable to demonstrate an improvement in hemodynamic variables at rest after prazosin therapy and have suggested that the beneficial effects of prazosin in patients with CHF may only be evident during exercise. In the present study, prazosin caused no demonstrable improvement in left ventricular ejection fraction or volumes at peak exercise when compared with placebo after 1 or 6 months of therapy.

Exercise variables: Neither exercise work load nor exercise duration improved after prazosin therapy in the present study at 1, 3, or 6 months. These observations are in agreement with those reported by Harper et al[25] after 4 weeks of double-blind prazosin therapy, but differ from those reported by Colucci et al[12] and Aronow et al.[24] It is of interest that total exercise duration actually tended to increase in the placebo-treated group rather than the prazosin-treated group of patients in the present study, although this difference was not significant. This observation suggests that our inability to demonstrate a beneficial effect from prazosin on total exercise duration does not represent a type II statistical error.

Neurohumoral variables: Plasma norepinephrine levels, which provide an index of the activity of the sympathetic nervous system,[30] are generally markedly elevated in patients with CHF.[31] Since a pure alpha-adrenergic antagonist such as prazosin has no intrinsic vasodilating actions, it has been suggested that its efficacy may depend on the degree of sympathetic tone, that is, that patients with severe CHF and markedly

elevated sympathetic tone may be more responsive than those with mild CHF, who generally have less sympathetic tone.[32] In this regard it is worth noting that the levels of plasma norepinephrine at rest in the prazosin-treated patients (790 ± 280 pg/ml, range 489 to 1,389) (Table IV) are similar to those reported by Levine et al[31] and considerably higher than those reported by Colucci et al.[32] Thus, the patients in the present study are precisely those in whom one might have anticipated a beneficial response from prazosin. An increase in plasma norepinephrine levels, both at rest and during exercise, has been reported with chronic prazosin therapy.[10,11,13,32] Indeed, an increase in vascular tone resulting from this increase in plasma norepinephrine level is one of the mechanisms that has been suggested to explain the development of tolerance to prazosin. Although plasma norepinephrine levels were higher after 4 weeks of therapy than at baseline in the prazosin-treated group in the present study, this difference was not significant (Table IV). After 26 weeks of therapy, plasma norepinephrine levels at rest were similar to those at baseline. Prazosin also caused no significant increase in plasma norepinephrine at peak exercise. Plasma epinephrine levels in the present study are also similar to those reported by Levine et al[31] and did not change significantly in response to prazosin, either at rest or during peak exercise. Both plasma norepinephrine and epinephrine levels increased in response to exercise to levels similar to those reported by Francis et al.[33]

The levels of plasma renin activity at rest in the present study are similar to those reported by Dzau et al[34] in patients with well-compensated CHF. Prazosin caused no demonstrable increase in plasma renin activity when compared with placebo. However, in both groups of patients plasma renin activity increased slightly but significantly with time. Body weight also increased with time in both groups of patients. These findings may therefore be interrelated.

Limitations and implications of the study: This study is the first double-blind, randomized, placebo-controlled study of the effects of prazosin in patients with CHF, both at rest and during exercise, in a well-matched, compliant group of patients extending over several months. However, it has certain limitations. First, the effect of prazosin was assessed using noninvasive rather than invasive techniques. We[19] and other workers[35] have previously demonstrated that noninvasive techniques, such as radionuclide ventriculography, are less sensitive than invasive techniques for assessing the hemodynamic changes produced by a vasodilator agent in a patient with CHF and a dilated left ventricle. However, while we[19] were able to demonstrate a significant reduction in end-diastolic and end-systolic volumes ($p < 0.001$) and an increase in left ventricular ejection fraction ($p < 0.005$) in response to nitroprusside, no such response could be demonstrated with prazosin despite meticulous care to ensure consistent background subtraction and definition of the region of interest. It is therefore possible that more subtle hemodynamic changes due to prazosin might have been detected with invasive techniques. However, if such hemodynamic changes occurred, they did not result in any improvement in symptoms. Second, treadmill exercise testing using a modified Naughton protocol with direct measurement of oxygen consumption[36] may be a more sensitive method of assessing changes in exercise capacity than bicycle ergometry in patients with CHF. This was not done in the present study since it would have precluded simultaneous radionuclide ventriculography during exercise. Validation of the achievement of maximum exercise by metabolic measurements, a more objective endpoint than fatigue, was therefore not possible. Third, the optimal daily dosage of prazosin is in dispute. Our daily dosage of 20 mg/day is similar to that used by Colucci et al,[12] higher than that used by some,[24,25] and lower than that used by other investigators.[9] Thus, it is possible that different results might have been obtained with either a higher or lower dosage. Finally, the designated level of statistical significance merits comment. Since multiple comparisons were performed on a large number of variables, a p value of 0.05 is not sufficiently stringent. We, therefore, arbitrarily set a p value of 0.01 as significant. In a recent comparable study[37] in which fewer variables were compared, other investigators set the level of significance at $p < 0.005$ (0.05 divided by the number of variables) based on the Bonferroni adjust-

TABLE IV Neurohumoral Variables

	B	Day 2	4 Weeks	12 Weeks	26 Weeks
			Prazosin Group		
R Epinephrine (pg/ml)	57 ± 31	. . .	69 ± 38	. . .	71 ± 74
Ex Epinephrine (pg/ml)	164 ± 115	. . .	198 ± 196	. . .	216 ± 172
R Norepinephrine (pg/ml)	790 ± 280	. . .	1,413 ± 1,030	. . .	875 ± 638
Ex Norepinephrine (pg/ml)	2,262 ± 1,474	. . .	3,432 ± 2,593	. . .	3,763 ± 3,179
Supine PRA (ng A_1/ml/h)	2.2 ± 1.3	3.6 ± 2.4	2.8 ± 2.2	3.7 ± 2.5	2.3 ± 2.3
Erect PRA (ng A_1/ml/h)	3.5 ± 2.5	5.9 ± 4.3	4.9 ± 3.9	5.7 ± 3.9	2.7 ± 1.8
			Placebo Group		
R Epinephrine (pg/ml)	97 ± 72	. . .	67 ± 42	. . .	93 ± 49
Ex Epinephrine (pg/ml)	234 ± 167	. . .	190 ± 117	. . .	339 ± 241
R Norepinephrine (pg/ml)	749 ± 315	. . .	772 ± 596	. . .	900 ± 361
Ex Norepinephrine (pg/ml)	1,997 ± 1,033	. . .	2,208 ± 1,646	. . .	2,767 ± 558
Supine PRA (ng A_1/ml/h)	1.8 ± 1.4	2.5 ± 2.1	3.0 ± 3.0	3.1 ± 2.1	1.9 ± 1.6
Erect PRA (ng A_1/ml/h)	2.1 ± 1.3	4.2 ± 2.7	3.9 ± 3.8	4.3 ± 2.5	2.9 ± 1.9

A_1 = angiotensin I; B = before therapy; Day 2 = after 3 doses of therapy; PRA = plasma renin activity; R = resting; other abbreviations as in Table I.

ment. However, even when the level of significance is set at the 0.05 level, there is no objective evidence of improvement in response to prazosin therapy at any point in time in our group of patients. These observations suggest that prazosin is not generally useful in the long-term management of a group of patients with CHF.

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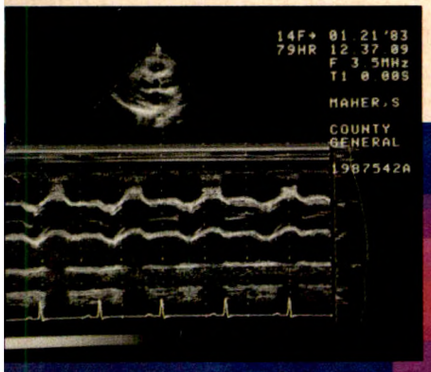

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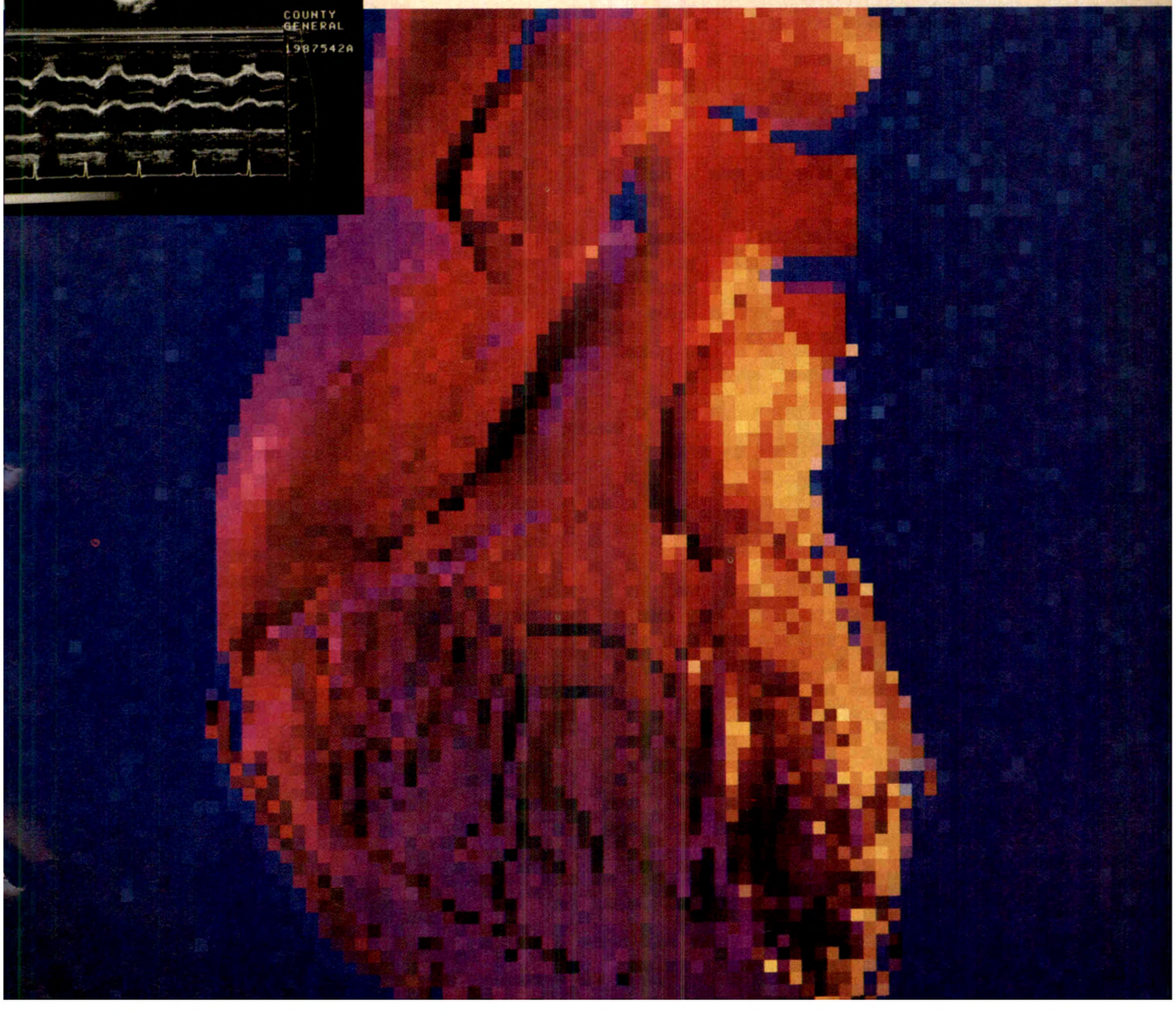

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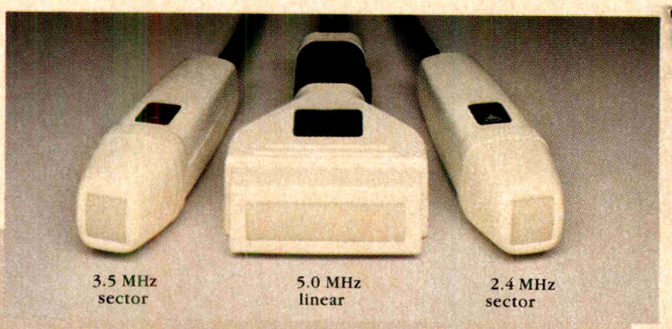

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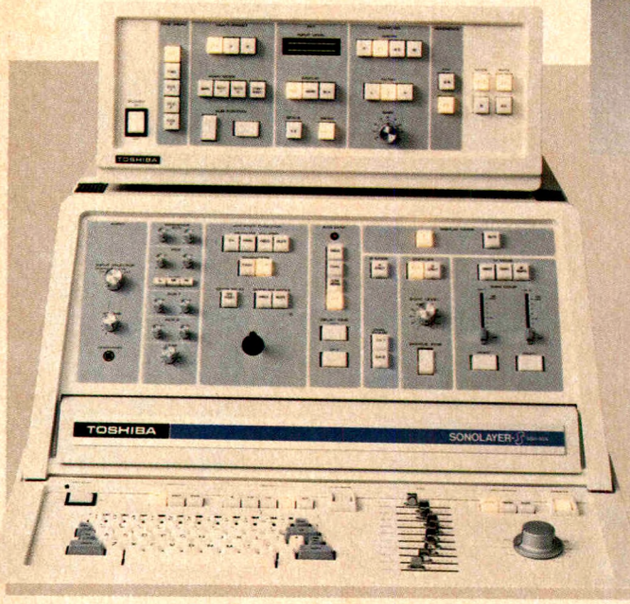

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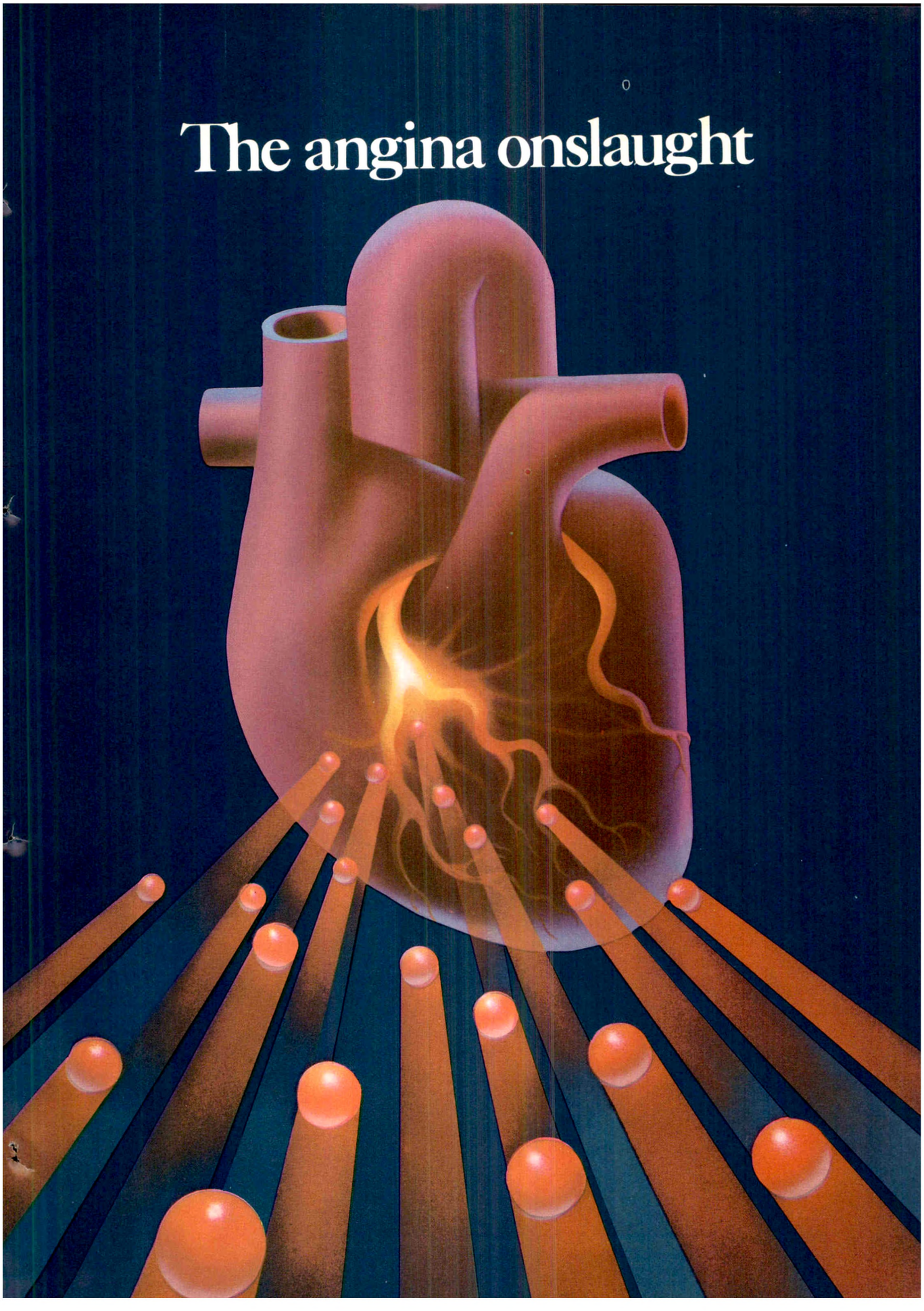

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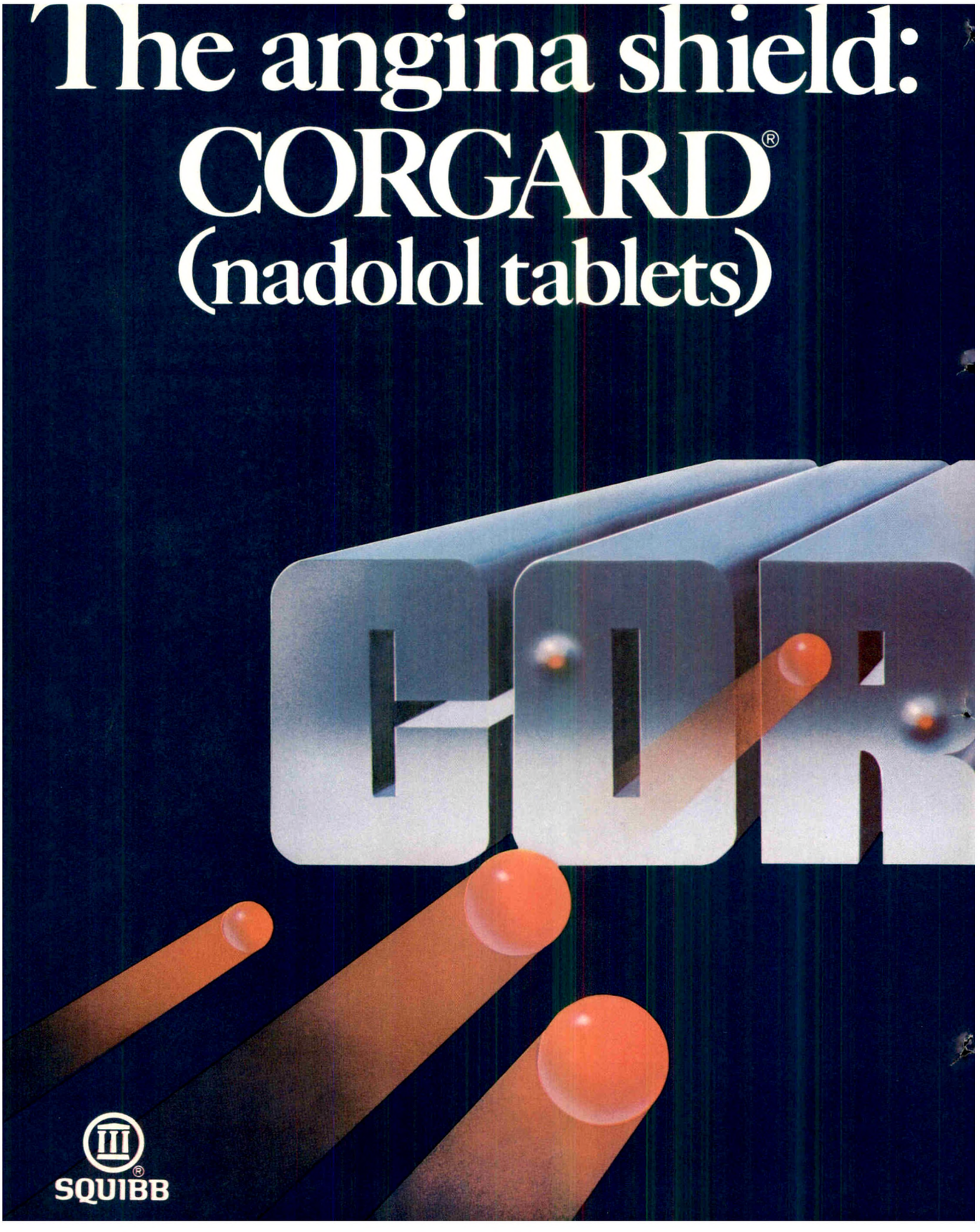

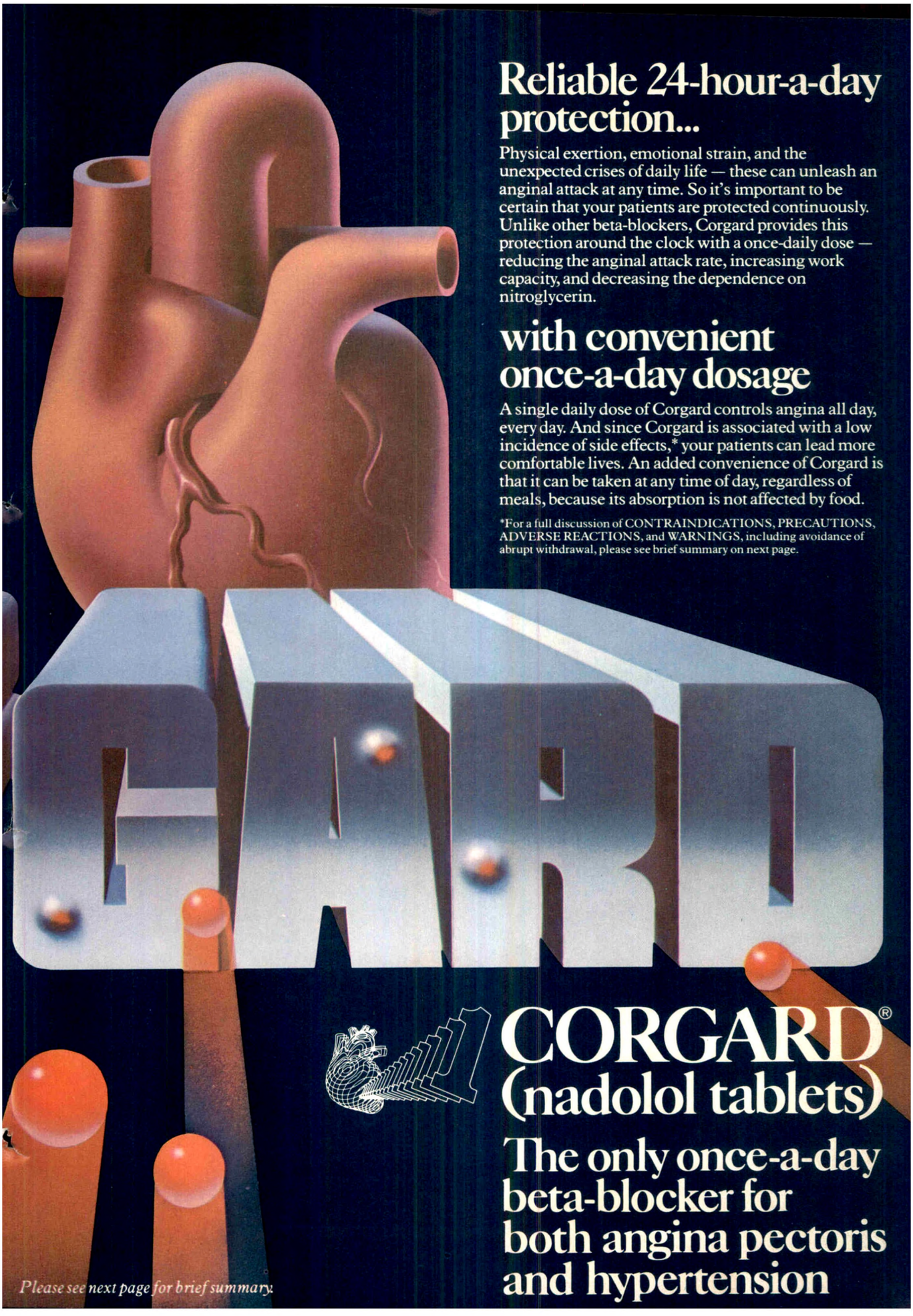
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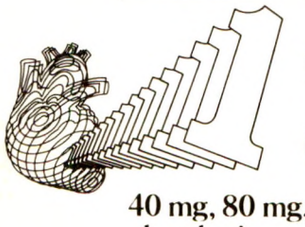

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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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Acute Hemodynamic Effects of Endralazine: A New Vasodilator for Chronic Refractory Congestive Heart Failure

ARSHED A. QUYYUMI, MB, MRCP, DONALD WAGSTAFF, and THOMAS R. EVANS, FRCP

Invasive hemodynamic measurements were made in 10 supine patients with chronic refractory congestive heart failure (CHF) due to ischemic heart disease or cardiomyopathy before and after oral administration of a new arteriolar vasodilator, endralazine. In 9 patients, a 10 mg dose of endralazine produced maximal increases in cardiac and stroke volume indexes of 56 and 41%, respectively, with a 45% reduction in total systemic resistance. After a 5 mg dose of endralazine, cardiac index increased maximally by 38% and stroke volume index by 34%, with a 31% decrease in total systemic resistance. Mean arterial pressure decreased 11 ± 4 mm Hg (mean ± standard error of mean) with the 5 mg dose and 17 ± 5 mm Hg after the 10 mg dose. There were no significant changes in the right atrial, pulmonary arterial, or pulmonary capillary wedge pressures. After administration of a single dose of endralazine, statistically significant hemodynamic changes were observed from 1 to 8 hours with peak responses at 3 to 4 hours. These observations suggest that endralazine has hemodynamic properties similar to those of its structural analog, hydralazine. However, endralazine metabolism is largely independent of the patients' acetylator status, and no cases of systemic lupus erythematosus have been reported after long-term oral administration. These findings suggest that endralazine may be an efficacious drug that is potentially safer than hydralazine in the treatment of chronic CHF.

Many studies have demonstrated the beneficial effects of vasodilators in chronic refractory congestive heart failure (CHF).[1–11] Several drugs are now available for clinical use, but all have major disadvantages. Long-acting nitrates reduce left ventricular filling pressure and are safe to administer but have a minimal effect on cardiac output.[6] Prazosin, a powerful arteriolar vasodilator, is associated with development of tolerance,[7,8] and minoxidil can cause hirsutism.[9,12] The dose of oral hydralazine required to produce optimal hemodynamic effects varies widely,[13] dependent in part on the patients' acetylator status. The incidence of antinuclear factor conversion at higher dose levels of hydralazine increases,[14–16] and a recent study suggested that tolerance to hydralazine may develop after long-term administration.[17] The search for alternative vasodilator agents largely free of serious side effects therefore continues.

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Endralazine (BQ22-708) is 6 benzoyl-3-hydrazino-5,6,7,8-tetrahydropyrido-4,3-c pyridazine mesilate.[18,19] It is structurally related to hydralazine (Fig. 1). Endralazine is metabolized chiefly by combination with endogenous ketones to form hydrazones.[20] These reactions are completely independent of the patient's acetylator status.[21,22] Several studies[20–25] in hypertensive patients have demonstrated the efficacy of endralazine as a powerful arteriolar dilator. No hypertensive patients treated with endralazine for up to 3 years have developed systemic lupus erythematosus.[20] Endralazine appears to have potentially less toxicity and a narrower effective dose range than many other vasodilators. This study was undertaken to determine its acute effects when administered orally to patients in chronic refractory CHF.

Methods

Patients: Ten patients, 9 men and 1 woman (age range 36 to 75 years [mean 62]) with chronic CHF of >3 months' duration, were studied. Nine patients had CHF secondary to proven ischemic heart disease demonstrated by coronary arteriography or documented previous myocardial infarction. One patient had alcoholic cardiomyopathy. Nine patients had sinus rhythm, 1 had atrial fibrillation (Patient 8), and 1 (Pa-

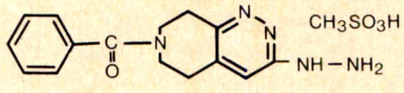
tient 7) had moderate mitral regurgitation. All patients were taking increasing doses of diuretic drugs with or without digoxin and vasodilators over the preceding months. Six patients were in New York Heart Association[26] class III and 3 were in class IV.

Hemodynamic measurements: A thermodilution pulmonary arterial catheter (model 7Fr, Instrumentation Laboratories) was introduced percutaneously through the subclavian vein under fluoroscopic control. Arterial pressure was measured directly with a soft Teflon® (Abbocath-T intravenous #21) radial artery cannula. Cardiac output was measured in triplicate using the thermodilution technique with Instrumentation Laboratories Cardiac Output Computer 701 and an ISCI/OMP-powered injector. Pressures were measured using a Hewlett-Packard monitor and transducers, and mean pressures integrated electronically. After all invasive procedures were completed, hemodynamic measurements were made at 15-minute intervals until 2 consecutive readings were obtained with a variation of <10%. These measurements included heart rate (HR), mean arterial pressure (AP), mean pulmonary arterial (PA), mean pulmonary capillary wedge (PCWP), and mean right atrial (RAP) pressures, and cardiac output (CO).

ENDRALAZINE: BQ 22-708

Chemical structure:

6-benzoyl-3-hydrazino-5,6,7,8-tetrahydropyrido-(4,3-c)-pyridazine mesylate



Molecular formula:

$C_{14}H_{15}N_3SO_3H$

HYDRALAZINE:

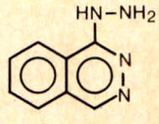


FIGURE 1. Molecular structure of endralazine and hydralazine.

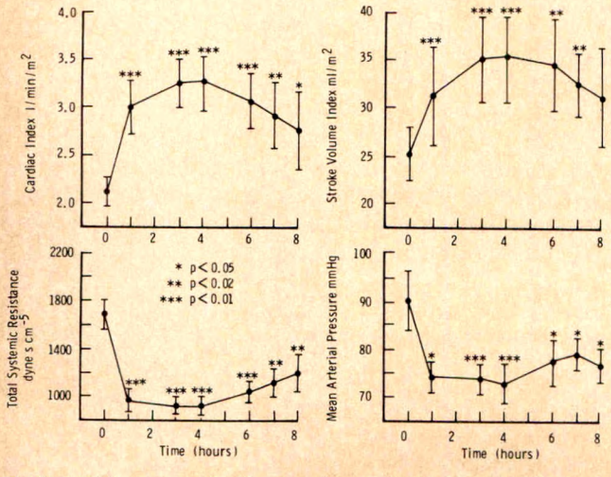


FIGURE 2. Hemodynamic changes observed with 10 mg oral dose of endralazine.

Hemodynamic variables were derived as follows: Cardiac index (liters·min^{-1} m^{-2}) = cardiac output ÷ body surface area; stroke volume index (ml·min^{-1} m^{-2}) = (cardiac index ×1,000) ÷ HR; total systemic resistance (dynes s cm^{-5}) = 80 × (mean AP − mean RAP) ÷ CO; total pulmonary resistance (TPR) (dynes s cm^{-5}) = 80 × (mean PA) ÷ CO; pulmonary arteriolar resistance (PAR) (dynes s cm^{-5}) = 80 × (mean PA − mean PCWP) ÷ CO; stroke work index (SWI) (g − m·m^{-2}) = SVI (AP − PCWP) × 0.0136.

Statistical analysis was performed using the Wilcoxon matched-pairs signed-rank test.

Drug administration: Two days before the study, all diuretic agents and vasodilators were stopped but digoxin was given at the end of the study each day. Nine patients were given a 10 mg dose of endralazine orally after food following baseline hemodynamic measurements. The patients remained supine throughout the study, hemodynamic measurements being made at 1, 3, 4, 5, 6, and 8 hours after drug administration. One of the 9 patients (Patient 2) had measurements made over 4 hours only. The following day, 9 patients (Patients 1, 2, and 4 to 10; Table I) received a 5 mg dose of endralazine orally, and measurements were made for at least 4 hours at hourly intervals. The study was discontinued at 4 hours because previous experience with the 10 mg dose had shown maximal effect at 3 to 4 hours. In 4 patients (Patients 1, 2, 5, and 6) there was no significant difference between the hemodynamic changes observed with the 5 mg dose compared with the 10 mg dose. Therefore these patients were given a 2.5 mg dose of oral endralazine and hemodynamic measurements were made over the next 4 hours.

Results

After administration of 10 mg of endralazine in 9 patients, significant increases in cardiac output and stroke volume were evident within 1 hour, with concomitant decreases in total systemic resistance (Fig. 2). The effect was maximal 3 to 4 hours after the dose, remaining significant even after 8 hours (Table I, Fig. 2). The 5 mg dose in 9 patients produced slightly smaller but similar significant changes (Table II, Fig. 3). The

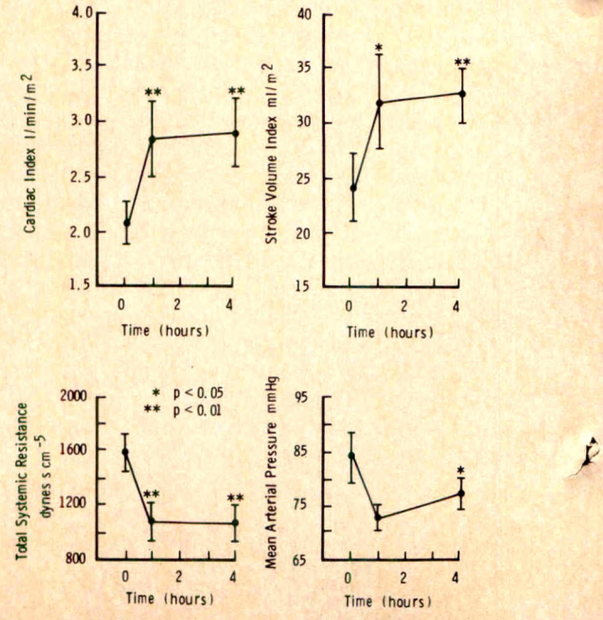


FIGURE 3. Hemodynamic changes observed with 5 mg oral dose of endralazine.

TABLE I Hemodynamic Results Before and 4 Hours After Oral Administration of 10 mg of Endralazine

Patient		HR	MAP	CI	SVI	SWI	TSR	MPA	PCWP	RAP	TPR	PAR
1	C	100	100	2.6	26	26.5	1,054	38	25	14	691	236
	E	105	70	2.6	25	17	1,031	40	20	12	712	356
2	C	100	75	1.8	18	9	1,672	60	38	6	1,454	533
	E	107	70	3.1	29	12.6	844	55	38	12	800	247
3	C	91	95	2.8	30.5	34	1,283	22	13	5	314	128
	E	100	70	4.1	41	32	581	24	13	−0.5	198	91
4	C	90	82	1.6	18	12	2,049	41	33	9	1,160	225
	E	100	78	2.4	24	14.6	1,284	44	33	9	819	205
5	C	87	88	1.6	19	19	2,000	27	16	8	680	275
	E	89	78	2.8	31	27	1,037	24	14	8	355	148
6	C	75	75	2.4	32	27	1,327	19	12	7	370	136
	E	87	48	4.4	50	30	512	15	4	0	160	96
7	C	75	133	2.5	33	51	2,167	33	19	3	383	233
	E	86	96	4.9	57	59	719	27	20	10	225	92
8	C	56	81	2.0	36	34	1,693	22	11	6.5	500	250
	E	66	82	2.8	42	40	1,245	23	12	7	381	182
9	C	105	81	1.5	14.5	10	1,886	44	29	15	1,257	429
	E	107	66	2.1	20	20	1,140	38	22	11	788	332
Mean	C	86 ± 5	90 ± 6.1	2.08 ± 0.16	25.2 ± 2.7	25 ± 4.6	1,681 ± 129	34 ± 4.4	21.8 ± 3.3	8.1 ± 4	757 ± 142	272 ± 44
± SEM	E	94 ± 4.5	73 ± 4.3	3.24 ± 0.32	35.4 ± 4.2	28 ± 5	933 ± 94	32.2 ± 4.2	19.6 ± 3.5	7.6 ± 1.6	493 ± 94	194 ± 34
Change		+8.8%	−18.8%	+55.8%	+40.5%	+13%	−44.6%	−5.3%	−10.1%	−6%	−33.2%	−28.7%
p		<0.01	<0.01	<0.01	<0.01	NS	<0.01	NS	NS	NS	<0.01	NS

C = pretreatment control; CI = cardiac index; E = 4 hours after 10 mg oral dose of endralazine; HR = heart rate (beats/min); MAP = mean arterial pressure; MPA = mean pulmonary arterial pressure; NS = not significant; PAR = pulmonary arteriolar resistance; PCWP = mean pulmonary capillary wedge pressure; RAP = mean right atrial pressure; SEM = standard error of the mean; SVI = stroke volume index; SWI = stroke work index; TPR = total pulmonary resistance; TSR = total systemic resistance. All pressures given in mm Hg; resistances given in dynes s cm^{-5}.

TABLE II Hemodynamic Results Before and 4 Hours After Oral Administration of 5 mg of Endralazine

Patient		HR	MAP	CI	SVI	SWI	TSR	MPA	PCWP	RAP	TPR	PAR
1	C	95	90	2.0	21.5	19	1,645	40	25	18	914	342
	E	100	72	2.6	26	17	1,054	38	25	14	691	236
2	C	100	75	1.8	18	9	1,672	60	38	6	1,454	533
	E	100	70	2.9	29	12.6	981	57	38	5	860	287
3	C	86	73	1.8	21	13.7	1,600	37	25	6	900	280
	E	100	76	2.0	20	14.7	1,470	40	22	8	865	389
5	C	88	95	1.8	20.5	21.2	1,980	29	19	8	660	228
	E	89	83	2.3	26	24.8	1,333	28	13	8	498	267
6	C	88	75	3.0	34	32.4	992	17	5	8	251	178
	E	84	77	4.0	48	45.7	778	17	7	7	188	111
7	C	75	108	2.6	36	46	1,522	30	14	11	471	235
	E	88	91	4.3	49	54	784	28	10	8	264	170
8	C	60	76	2.2	36	29.9	1,435	23	15	8	485	168
	E	58	77	2.7	47	42.2	1,186	21	11	7	356	169
9	C	107	83	1.5	14	10.9	2,124	43	26	11	1,269	486
	E	110	75	2.5	23	17.2	1,118	34	20	10	588	242
10	C	118	76	1.6	14	9.7	1,425	35	25	19	875	250
	E	124	72	2.2	18	11.8	1,153	30	24	10	558	112
Mean	C	90.8 ± 5.7	83.4 ± 4	2.03 ± 0.16	23.8 ± 3.0	21.3 ± 4.2	1,579 ± 110	34.9 ± 4.2	21.4 ± 3	10.6 ± 1.6	809 ± 129	300 ± 42
± SEM	E	94.8 ± 6.1	77 ± 2.2	2.8 ± 0.27	31.8 ± 4.2	26.7 ± 5.4	1,095 ± 76	32.6 ± 3.9	18.9 ± 3.2	8.6 ± 0.9	541 ± 81	220 ± 30
Change		+4.4%	−7.7%	+38%	+33.6%	+25%	−30.7%	−6.7%	−11.7%	−19%	−33%	−30.7%
p		<0.05	<0.05	<0.01	<0.01	<0.01	NS	NS	NS	<0.01	<0.05	

Abbreviations as in Table I.

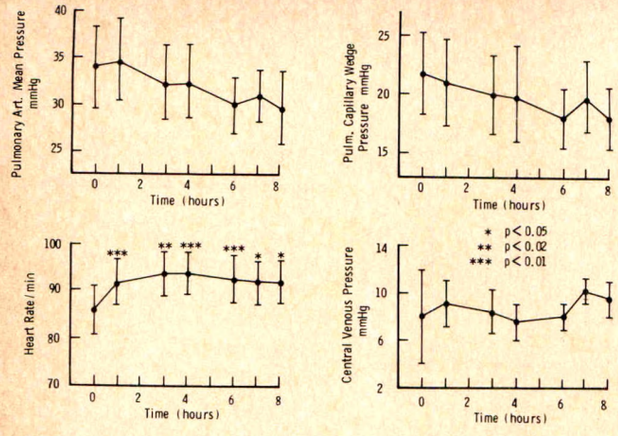


FIGURE 4. Hemodynamic changes observed with 10 mg oral dose of endralazine. Art. = arterial; Pulm. = pulmonary.

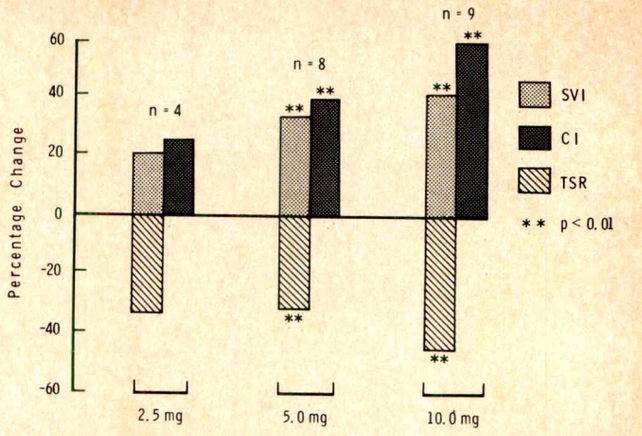


FIGURE 5. Percent hemodynamic changes observed with 2.5, 5, and 10 mg oral doses of endralazine. CI = cardiac index; SVI = stroke volume index; TSR = total systemic resistance.

decrease in mean arterial pressure and the increase in heart rate were significantly smaller with the 5 mg dose. No significant changes occurred in pressures in the right side of the heart (Fig. 4). Four patients receiving a 2.5 mg dose demonstrated smaller increases in cardiac and stroke volumes, but changes in arterial pressure and heart rate were insignificant (Fig. 5).

Discussion

Endralazine has been extensively evaluated in animal studies and has been demonstrated to have powerful arteriolar dilating action.[20,27,28] In hypertensive patients, endralazine has been found to reduce blood pressure as effectively as hydralazine and prazosin.[19,21,25] On a weight-for-weight basis it is approximately 4 to 5 times as potent as hydralazine.[20,28]

Hemodynamic changes were noted with doses ranging from 2.5 to 10 mg. Most patients achieved considerable hemodynamic improvement with the 5 mg dose of endralazine. In 2 patients (Patients 6 and 7) the 10 mg dose of endralazine produced a marked decrease in arterial pressure and increase in heart rate denoting excessive vasodilatation. Patients who were initially hypertensive (Patients 1 and 7) also had a greater than average reduction in mean arterial pressure. The patients who received the 2.5 mg dose of endralazine showed a smaller decrease in systemic resistance and a smaller increase in cardiac output than those receiving the larger doses (Fig. 5). These results suggest that for most patients in refractory cardiac failure, an optimal hemodynamic response with minimal adverse effects will be obtained with the 5 mg dose of endralazine (Table II). Oral endralazine is rapidly absorbed, with obvious hemodynamic effects within 1 hour of administration reaching a maximum at 3 to 4 hours. The plasma half-life of endralazine is much longer than that of hydralazine, and in hypertensive patients a twice-daily dose may provide adequate control.[20] Fixation to vessel walls and subsequent slow release may explain the prolonged in vivo action of hydralazine,[29–31] and a similar phenomenon has been demonstrated using carbon-14–labeled endralazine in animals.[20]

Several studies in hypertension[20–22] have clearly shown that acetylator status has no effect on the dose of endralazine required, whereas it profoundly influences the dose of hydralazine needed for a therapeutic effect[16]: this is an important advantage of endralazine, which will have a narrower dose range than hydralazine.

Throughout this study patients remained supine and no adverse effects were noted. No patient had any hypotensive symptoms, and only 1 patient experienced facial flushing with a 10 mg and not with a 5 mg dose of endralazine. Long-term studies in hypertensive patients have confirmed the absence of serious side effects or tolerance.[20,22,24] Flushing and edema were the most commonly noticed adverse effects, the latter responding to the addition of a diuretic drug. None of the 224 patients treated for approximately 1 year had any clinical manifestations of systemic lupus erythematosus.[20] Two patients had significant antinuclear antibody titres in the serum, but there were no increases in these levels with continuation of endralazine therapy. The hydrazine radical on both the molecules of hydralazine and endralazine is thought to be immunogenic when combined with collagen.[32] The difference in metabolism of the 2 drugs and the higher potency of endralazine minimizes the exposure of the hydrazine radical to collagen even after prolonged treatment.

Endralazine is an orally effective powerful arteriolar dilator and after acute administration in this study it has been shown to produce an increased cardiac output in patients with chronic refractory CHF. It has no significant venodilating action. Essentially 3 factors limit the usefulness of hydralazine in some patients with chronic CHF: (1) the wide variability in the dose of hydralazine required for therapeutic effect,[13] (2) the risk of developing systemic lupus erythematosus at larger dose levels,[14–16] and (3) tolerance after long-term treatment.[17] Endralazine, which has a different metabolism, appears superior to hydralazine for at least 2 reasons. Unless tolerance to endralazine develops on long-term therapy, its narrower dose range and freedom

from immunologic side effects suggest it is safer and potentially superior to hydralazine. Long-term studies to evaluate the sustained efficacy of endralazine in refractory CHF at rest and on exercise are required and are being undertaken at this center.

Acknowledgment: We are grateful to Cecil Symons, MD, FRCP, for allowing us to study patients under his care, and to Sandoz Pharmaceuticals for financial support.

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Exercise Intolerance in Patients With Chronic Left Heart Failure: Relation to Oxygen Transport And Ventilatory Abnormalities

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Circulatory, metabolic, and ventilatory responses to maximal and submaximal symptom-limited exercise were studied in 13 patients with chronic stable heart failure. Maximal exercise was sustained 6.5 ± 0.6 minutes (mean ± standard error of the mean) and increased minute oxygen consumption ($\dot{V}O_2$) to 940 ± 65 ml/min, whereas submaximal exercise was sustained for 15.4 ± 2.3 minutes and increased $\dot{V}O_2$ to 825 ± 49 ml/min (both $p < 0.01$ compared with maximal exercise). Both exercise protocols were terminated because of fatigue and both were associated with reduced cardiac output relative to $\dot{V}O_2$, marked systemic oxygen extraction (80 ± 2% maximal versus 78 ± 2% submaximal) and similarly elevated blood lactate concentrations (37 ± 4 mg/dl maximal versus 36 ± 4 mg/dl submaximal), suggesting inadequate oxygen delivery to working muscle. Minute ventilation during both types of exercise was also more than twice normal relative to carbon dioxide production. However, during submaximal exercise, dyspnea was noted in only 3 patients despite these ventilatory abnormalities. During maximal exercise, dyspnea was noted in 11 patients but did not force termination of exercise or preclude achievement of marked systemic oxygen extraction and lactate production. These data suggest that patients with chronic stable cardiac failure are limited during both maximal and submaximal exercise primarily by inadequate oxygen transport to working muscle.

Patients with chronic heart failure are frequently limited during exertion even when they have no symptoms at rest.[1–3] Several investigators have suggested that this exercise intolerance is primarily due to inadequate oxygen transport to working muscle.[3–6] This hypothesis is supported by the observation that maximal exercise in patients with chronic heart failure is associated with progressive increases in blood lactate concentration and oxygen extraction, suggesting inadequate oxygen availability in working skeletal muscle.[3,4,7]

Other investigators have suggested that the exercise intolerance of these patients may partially be due to elevated intrapulmonary pressure and exertional dyspnea,[2,8,9] particularly during normal daily activities, most of which involve submaximal exercise. During submaximal exercise, oxygen transport to working muscle may be adequate because the oxygen demands of muscle are lower than they are during maximal exercise. Submaximal exercise also can be sustained for substantially longer periods of time than maximal exercise. Therefore, intrapulmonary pressure may remain elevated much longer and may produce more severe ventilatory abnormalities and breathlessness than those observed during maximal exercise. However, whether this is the case remains uncertain because respiratory function and oxygen transport during submaximal exercise have not previously been characterized in patients with chronic heart failure.

The present study was undertaken to determine whether patients with chronic heart failure are limited during exercise by oxygen transport abnormalities or ventilatory abnormalities. We examined symptomatic, metabolic, and ventilatory responses to both maximal and submaximal exercise in patients with chronic stable heart failure due to left ventricular dysfunction. We postulated that if exercise is limited by inadequate oxygen transport to working muscle, termination of exercise would be associated with exhaustion and metabolic evidence of inadequate muscle perfusion. Alternatively, if exercise is limited by the respiratory system, termination of exercise would be associated with dyspnea and ventilatory abnormalities without metabolic evidence of inadequate muscle perfusion.

Methods

Patients: Thirteen men with chronic functional class III heart failure and left ventricular dysfunction (ejection fraction 24 ± 7%) were studied (Table I). The mean age was 55 ± 5 years. All patients had a history of exertional fatigue despite the administration of digoxin and diuretics. All patients had a clinically stable condition with no history of worsening heart failure or a change in cardiac medication for 2 months; pe-

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TABLE I Hemodynamic and Metabolic Effects of Maximal and Submaximal Exercise in Heart Failure

		HR (beats/min)	$\overline{BP}$ (mm Hg)	PAP (mm Hg)	PWP (mm Hg)	CO (liters/min)	$\dot{V}O_2$ (ml/min)	$\dot{V}E$ (liters/min)	Lactate (mg/100 ml)	AVO_2 (ml/100 ml)	O_2 Ext (%)	Duration (min)	Symptom
1.	Base	86	96	52/30	25	2.8	318	11.4	10.0	11.2	61	...	Dyspnea
	Max	110	106	62/42	27	5.3	828	40.0	25.8	15.5	84	5′15″	Fatigue
	Base	96	96	40/30	20	3.2	326	12.6	11.7	10.6	59	...	Dyspnea
	Sub	114	108	60/40	30	4.7	710	32.0	21.9	15.1	82	6′	Fatigue
2.	Base	96	94	38/22	17	2.8	277	15.0	7.6	9.8	49	...	Dyspnea
	Max	128	98	42/30	25*	4.7	820	49.0	31.0	17.3	86	5′30″	Fatigue
	Base	92	100	34/26	21*	3.3	282	13.7	9.5	8.7	43	...	Dyspnea
	Sub	126	110	46/36	31*	4.6	750	43.7	36.2	16.5	82	8′	Fatigue
3.	Base	96	90	38/30	30	2.8	285	15.6	10.4	10.1	60	...	Dyspnea
	Max	150	102	55/45	40	5.6	782	54.0	23.5	13.9	82	4′15″	Fatigue
	Base	103	92	42/30	25	2.8	295	15.9	12.5	10.5	63	...	Dyspnea
	Sub	136	104	60/45	40	5.2	708	49.9	30.0	13.6	81	8′	Fatigue
4.	Base	87	110	60/30	30	3.5	320	22.9	12.2	9.1	57	...	Dyspnea
	Max	122	130	90/45	40	8.6	1,081	66.6	32.7	12.5	78	7′30″	Fatigue
	Base	88	110	62/40	30	3.8	344	17.7	13.2	9.0	56	...	...
	Sub	124	130	90/45	38	6.6	859	45.3	25.2	13.0	81	28′	Fatigue
5.	Base	96	78	28/20	11	4.1	267	10.9	8.5	6.6	43	...	Dyspnea
	Max	120	92	65/45	41	7.4	849	48.9	42.8	11.5	76	4′30″	Fatigue
	Base	90	74	22/12	8	4.0	258	10.8	15.6	6.4	42	...	...
	Sub	113	90	62/42	40	6.9	754	35.0	36.7	10.9	72	9′	Fatigue
6.	Base	88	115	53/32	30	2.5	227	11.8	12.5	9.2	51	...	Dyspnea
	Max	108	115	63/35	36	5.2	750	43.0	32.2	14.3	79	5′30″	Fatigue
	Base	89	89	50/30	30	2.5	217	8.7	14.6	8.7	49	...	...
	Sub	110	95	70/40	36	5.4	724	35.8	40.8	13.4	74	25′30″	Fatigue
7.	Base	99	100	50/35	27	3.2	274	15.9	8.9	8.7	51	...	Dyspnea
	Max	126	102	72/42	33	4.8	608	53.0	19.4	12.6	74	3′	Fatigue
	Base	105	94	65/35	25	2.9	267	16.5	9.8	9.3	55	...	...
	Sub	128	84	65/35	32	4.4	538	41.1	21.6	12.4	73	6′	Fatigue
8.	Base	89	102	45/25	27	3.3	273	13.1	6.7	8.4	47	...	Dyspnea
	Max	120	123	62/40	42	6.2	895	45.8	24.9	14.5	82	6′30″	Fatigue
	Base	84	104	38/28	25	3.9	307	14.1	15.9	7.8	44	...	...
	Sub	120	120	64/46	50	5.8	845	39.2	25.6	14.5	82	12′	Fatigue
9.	Base	101	78	25/16	12	3.0	214	7.6	23.2	7.1	36	...	...
	Max	150	96	70/48	44*	6.5	888	44.8	47.0	13.8	70	7′	Fatigue
	Base	94	73	25/15	11*	2.9	247	9.3	14.5	8.5	43	...	...
	Sub	156	93	72/46	42*	6.9	917	47.5	48.1	13.2	67	12′	Fatigue
10.	Base	73	78	43/22	27	3.0	231	11.0	8.0	7.6	50	...	Dyspnea
	Max	114	92	65/38	35	11.5	1,296	61.7	49.5	11.3	74	9′	Fatigue
	Base	72	78	45/22	32	3.3	230	21.1	17.1	7.0	46	...	...
	Sub	108	90	78/33	45	7.0	827	39.4	40.9	11.8	78	24	Fatigue
11.	Base	72	75	20/10	8	3.1	245	9.5	9.8	8.0	42	...	Dyspnea
	Max	144	82	60/48	46*	7.3	1,165	48.8	57.0	15.9	84	10′30″	Fatigue
	Base	83	75	22/12	10*	4.0	288	11.6	...	7.2	38	...	...
	Sub	144	90	60/48	46*	6.6	1,012	42.9	...	15.4	82	28′	Fatigue
12.	Base	102	70	28/22	18	3.9	370	12.8	16.6	9.5	45	...	Dyspnea
	Max	150	118	65/50	38	8.4	1,425	57.0	56.9	17.1	81	9′	Fatigue
	Base	102	68	28/18	15	3.6	372	13.1	17.1	10.5	50	...	...
	Sub	144	110	58/48	38	8.3	1,269	47.0	37.1	15.3	72	19′	Fatigue
13.	Base	72	98	52/25	25	2.5	221	8.2	7.8	8.9	48	...	...
	Max	120	110	76/41	41*	5.1	831	55.4	63.4	16.2	87	8′	Fatigue
	Base	78	82	52/25	25*	2.3	221	8.2	15.8	9.5	52	...	...
	Sub	120	95	76/40	40*	5.0	806	42.4	67.1	16.1	86	14′30″	Fatigue
Mean ± SE:	Base	89±3	91±4	...	22±2	3.1±0.1	271±13	12.7±1.1	11±1	8.8±0.4	49±2	...	...
	Max	128±4	105±4	...	38±2	6.7±0.6	940±65	51.4±2.1	37±4	14.3±0.6	80±2	6.5±0.6	...
	Base	91±3	87±4	...	22±2	3.3±0.2	281±13	13.3±1.1	14±1	8.8±0.4	49±2	...	...
	Sub	126±4	101±4	...	39±2	6.0±0.3*	825±49†	41.6±1.5†	36±4	13.7±0.5*	78±2*	15.4±2.3†	...

* $p < 0.05$ compared with maximal exercise.
† $p < 0.01$ compared with maximal exercise.
AVO_2 = arteriovenous oxygen difference; BP = blood pressure; CO = cardiac output; Ext = extraction; HR = heart rate; PAP = pulmonary arterial pressure; PWP = pulmonary wedge pressure; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = minute oxygen consumption.

ripheral edema, ascites, and pulmonary rales were not present at the time of the study. Left ventricular dysfunction was attributed to coronary disease in 8 patients and to idiopathic cardiomyopathy in 5.

Protocol: To acquaint the patient with the exercise protocol, trial maximal and submaximal exercise tests were performed the day before study. Exercise was performed on an upright bicycle ergometer (Monarch). For maximal exercise testing, exercise was begun at a work load of 20 W and increased every 3 minutes by 20 W to a symptomatic maximal level. Submaximal exercise testing was performed at 50% of the maximal work load.

The following day, a triple-lumen Swan-Ganz catheter was inserted through an antecubital vein and positioned in the pulmonary artery. A short polyethylene catheter was inserted in a radial artery. Twenty minutes after instrumentation, maximal exercise testing was performed. Resting oxygen consumption was measured continuously for 5 to 10 minutes before exercise and throughout exercise. Pulmonary artery and wedge pressure was recorded and pulmonary artery and arterial blood samples for oxygen saturation and lactate concentration were obtained at rest, 2.5 minutes into each stage of exercise, and at maximal exercise. Arterial blood samples for pH and partial pressure of carbon dioxide and

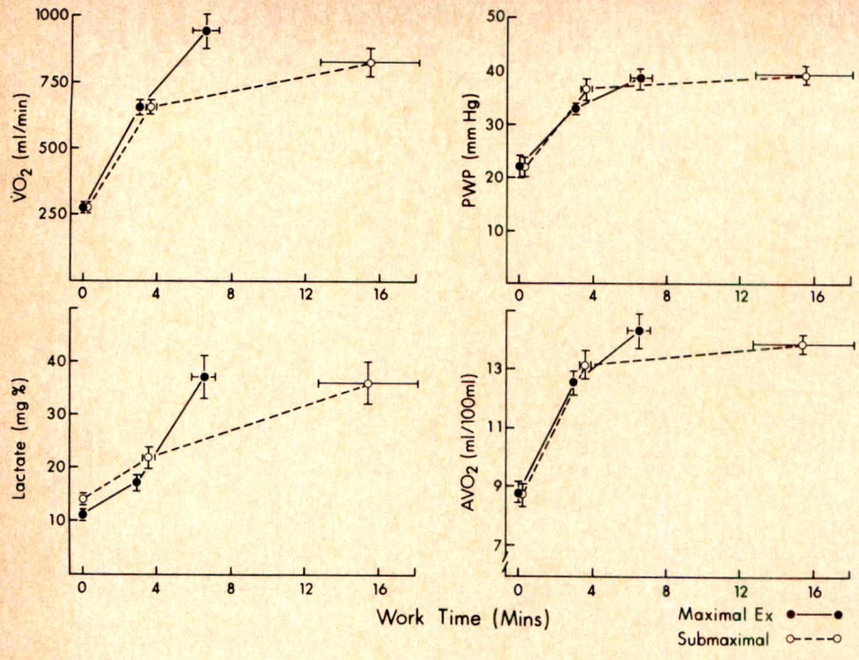

FIGURE 1. Effect of maximal and submaximal exercise (Ex.) on minute oxygen consumption ($\dot{V}O_2$), pulmonary wedge pressure (PWP), lactate, and arteriovenous oxygen difference (AVO_2). Mean ± standard errors are given at rest, for the first sampling period, and at peak exercise.

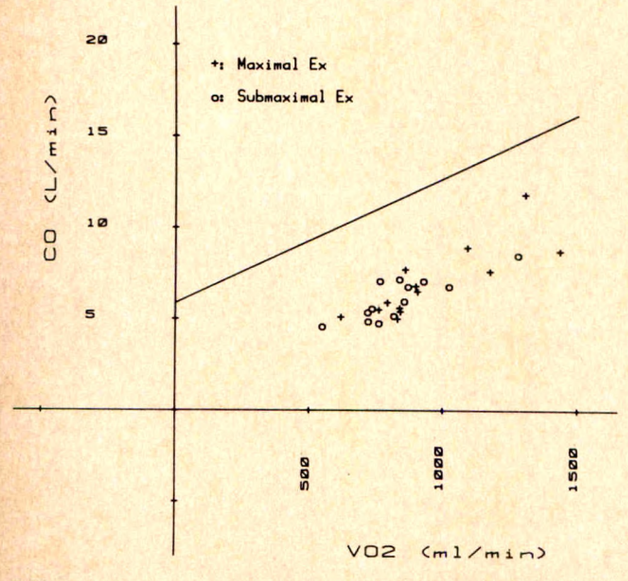

FIGURE 2. Relation of cardiac output (CO) to $\dot{V}O_2$ at peak maximal (+) and submaximal (0) exercise. The normal cardiac output response is indicated by the **solid line**.[26]

oxygen were obtained at rest and at maximal exercise in 9 patients.

After a 2-hour period of rest, submaximal exercise was performed at a fixed work load of 50% of the maximal work load achieved earlier in the day. Respiratory measurements were taken as noted previously. Hemodynamic measurements and blood samples were obtained at 3- or 4-minute intervals depending on the expected exercise duration. In 3 patients, pulmonary wedge pressure could not be obtained after initial baseline recordings. In these patients, pulmonary wedge pressure was estimated from pulmonary artery diastolic pressure by subtracting the resting pulmonary artery diastolic-wedge pressure gradient.

Measured variables: Minute oxygen consumption ($\dot{V}O_2$), minute carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were measured with a Beckman metabolic cart equipped with a Beckman OM-11 oxygen analyzer, Beckman LB-2 carbon dioxide analyzer, and a volume transducer. Respiratory gases were delivered first to a mixing chamber and then to a volume transducer and gas analyzer. Total expired volume and the average oxygen and carbon dioxide concentrations of expired gas were calculated every 30 seconds by a Model 1810 Monroe programmable calculator and used to calculate $\dot{V}CO_2$ and $\dot{V}O_2$. Results were printed on tape. Resting values reported represent the mean of values obtained over 5 to 10 minutes. The gas analyzers were calibrated at the beginning of each study with a 4% carbon dioxide/16% oxygen balanced nitrogen calibration gas.

Mean blood pressure was obtained by electronic integration of the phasic arterial pressure tracing. Arterial blood for lactate determination was deproteinized with cold perchloric acid and assayed with a spectrophotometric technique. Hemoglobin concentration was measured by a Coulter counter. Hemoglobin oxygen saturation was measured by a co-oximeter (Instrumentation Laboratories) precalibrated with human blood. Blood oxygen content was calculated as follows: hemoglobin × 1.34 ml oxygen/gram hemoglobin × percent oxygen saturation. Arteriovenous oxygen difference was calculated as arterial-pulmonary artery oxygen content. Oxygen extraction was calculated as the arteriovenous oxygen difference/arterial oxygen content. Cardiac output was calculated by the Fick principle as $\dot{V}O_2$/arteriovenous oxygen difference.

Statistical methods: Statistical analysis was performed by Student's *t* test for paired or unpaired data, as appropriate. Linear regression analysis was performed using the least-squares method. Data are expressed as mean ± standard error. A p value <0.05 was considered statistically significant.

Results

Results of this study are summarized in Table I and Figures 1 to 4. During maximal exercise, the peak work load achieved averaged 51 ± 16 W (range 20 to 80).

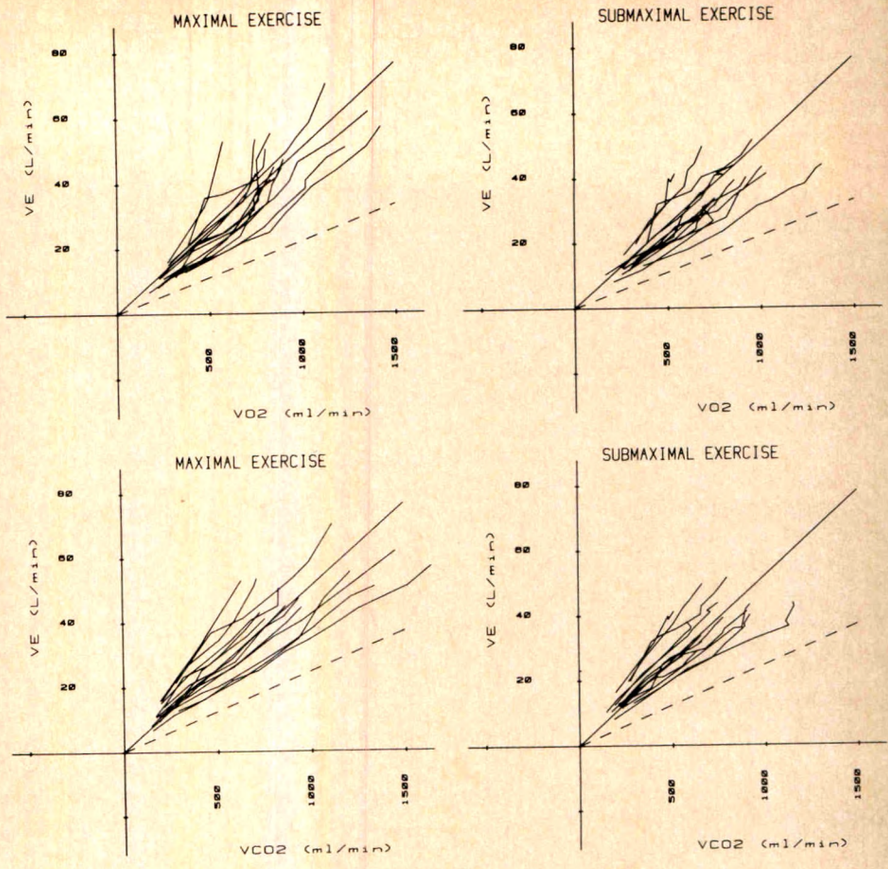

FIGURE 3. Relation of minute ventilation ($\dot{V}_E$) to $\dot{V}O_2$ and $\dot{V}CO_2$ during maximal and submaximal exercise. Normal ventilatory responses are indicated by the **broken lines**. The average slopes of the patients are indicated by the **solid lines**.

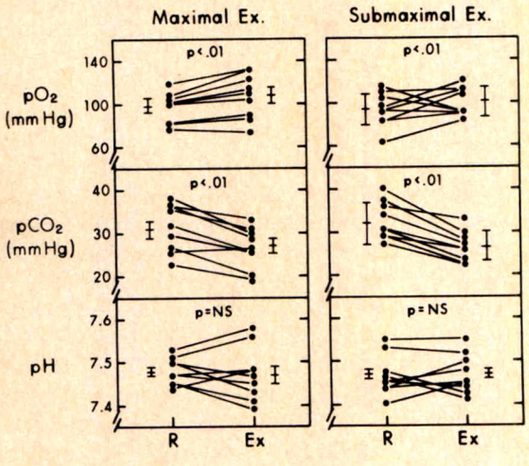

FIGURE 4. Effect of maximal and submaximal exercise (Ex.) on arterial partial pressure of oxygen (pO_2) and carbon dioxide (pCO_2) and pH. NS = not significant.

Submaximal exercise was performed at an average work load of 25 ± 8 W (range 10 to 40).

Maximal exercise: Maximal exercise was sustained for 6.5 ± 0.6 minutes and increased $\dot{V}O_2$ from 271 ± 13 to 940 ± 65 ml/min, cardiac output from 3.1 ± 0.1 to 6.7 ± 0.6 liters/min, and pulmonary wedge pressure from 22 ± 2 to 38 ± 2 mm Hg (Fig. 1). The peak cardiac output was reduced in all patients relative to $\dot{V}O_2$ (Fig. 2).[10,11] Exercise produced progressive elevations in lactate (11 ± 1 to 37 ± 4 mg/dl) and marked oxygen extraction (49 ± 2 to 80 ± 2%) (Fig. 1), consistent with inadequate oxygen delivery to working muscle. Exercise was terminated by leg fatigue in all patients, although 11 patients also reported moderate to severe dyspnea.

Minute ventilation during exercise was linearly related to $\dot{V}CO_2$ in all patients (r = 0.96 to 0.99) (Fig. 3). The slopes of these relations (0.051 ± 0.015 [mean ± standard deviation]) were nearly twice those reported in normal subjects (0.023 ± 0.005),[12,13] indicating both excessive ventilatory levels and increased ventilation of anatomic or physiologic dead space, or both.[14] Ventilatory levels were also excessive relative to $\dot{V}O_2$. Up to 20 to 50% of maximal $\dot{V}O_2$, minute ventilation was linearly related to $\dot{V}O_2$ with a slope of 0.051 ± 0.013 versus of 0.022 ± 0.012 in normal subjects.[12,13–15] At levels of $\dot{V}O_2$ above 50% of the maximal $\dot{V}O_2$, minute ventilation increased out of proportion to increases in $\dot{V}O_2$ because of buffering of lactate by bicarbonate and consequent release of carbon dioxide.[3,8,14]

Exercise increased the arterial pO_2 (98 ± 5 to 108 ± 7 mm Hg [$p < 0.01$]), decreased arterial pCO_2 (31 ± 2 to 27 ± 2 mm Hg [$p < 0.01$]), whereas pH remained unchanged (7.48 ± 0.01 to 7.47 ± 0.02 [p not significant]) (Fig. 4).

Submaximal exercise: In all patients, submaximal exercise was sustained substantially longer than maximal exercise (15.4 ± 2.3 minutes). Oxygen uptake in-

creased rapidly with the onset of exercise, thereafter increasing at a lesser pace. At the termination of exercise, both cardiac output and $\dot{V}O_2$ were significantly lower than during maximal exercise (6.0 ± 0.3 liters/min and 825 ± 49 ml/min, respectively). Peak cardiac output was reduced in all patients relative to $\dot{V}O_2$, as during maximal exercise (Fig. 2).

Despite lower work loads and oxygen uptake than those during maximal exercise, submaximal exercise produced progressive increases in blood lactate (14 ± 1 to 36 ± 4 mg/dl) and oxygen extraction (49 ± 2 to 78 ± 2%), suggesting inadequate oxygen availability in working muscle. Levels increased less rapidly than during maximal exercise (Fig. 1). However, exercise was terminated when lactate concentrations and oxygen extraction achieved levels comparable to those noted at termination of maximal exercise. Exercise was terminated by fatigue in all patients, with only 3 patients reporting moderate dyspnea.

Despite the lower incidence of symptomatic dyspnea than that during maximal exercise, pulmonary wedge pressure increased as rapidly as during maximal exercise (22 ± 2 to 39 ± 2 mm Hg) and remained elevated substantially longer (Fig. 1). However, the relation of minute ventilation to $\dot{V}O_2$ and $\dot{V}CO_2$ was comparable to that noted during maximal exercise; minute ventilation was linearly related to $\dot{V}O_2$ ($r = 0.94$ to 0.99) with a slope of 0.051 ± 0.016 (mean ± standard deviation) and to $\dot{V}CO_2$ ($r = 0.96$ to 0.99) with a slope of 0.052 ± 0.013 (Fig. 3). Peak minute ventilation reached was actually less than that during maximal exercise because of the lower levels of $\dot{V}O_2$ and $\dot{V}CO_2$ achieved. Changes in arterial blood gases during submaximal exercise were similar to those noted during maximal exercise (Fig. 4).

Discussion

Patients with chronic heart failure are frequently limited during exercise.[1–3] Recently, there has been great interest in identifying pharmacologic methods of improving the exercise capacity of such patients. To attain this objective, the mechanism responsible for the reduced exercise capacity must be identified. Accordingly, the present study was undertaken to investigate the mechanism of exercise intolerance in a specific subgroup of patients with heart failure, those with clinically stable, chronic heart failure who are without evidence of pulmonary alveolar or peripheral edema. Submaximal as well as maximal exercise was studied because most normal daily activities performed by such patients involve submaximal exercise. Work loads (10 to 40 W) undertaken during submaximal exercise protocols in the present study are equivalent to walking and housework and therefore comparable to exercise levels during normal daily activity.

Exercise limitation and oxygen transport: The results of the present study suggest that both submaximal and maximal exercise capacity of such patients is limited by the same factor: inadequate oxygen transport to working muscle. During both levels of exercise, exhaustion was the principal limiting symptom whether or not dyspnea was present. During both exercise protocols, progressive increases in blood lactate occurred, indicating inadequate oxygen availability in working muscle and increased anaerobic metabolic activity.[4,16,17] Moreover, submaximal and maximal exercise was terminated at nearly identical levels of lactate, suggesting that accumulation of a critical level of lactate in working muscle may have produced exhaustion by depressing muscle contractile force. In normal subjects performing exhaustive exercise of varying duration, a similar close relation between exhaustion and achievement of a critical level of lactate was noted unless exercise was extremely prolonged.[16]

The levels of oxygen extraction noted at the end of exercise further suggest that exercise was terminated because of exhaustion of oxygen transport to working muscle. During exercise, oxygen delivery to working muscle is determined by cardiac output and the capacity of muscle to extract oxygen.[18,19] These 2 factors increase simultaneously so as to optimize oxygen delivery, exhaustion of oxygen transport mechanisms coinciding with exhaustion of oxygen extraction.[18–20] In untrained normal subjects, this exhaustion occurs at a maximal oxygen extraction of 70 to 80%.[18–20] Levels of oxygen extraction in the present study were equal to or exceeded these levels when cardiac output was reduced. This finding suggests that the capacity of the circulatory system to deliver oxygen to working muscle by increasing either cardiac output or oxygen extraction was exhausted.

Previous investigators have also noted that in patients with chronic heart failure, elevated blood lactate levels, marked oxygen extraction, and a plateau in oxygen uptake frequently develop during maximal exercise.[3,4,7] They also concluded that maximal exercise capacity in patients with heart failure is limited by oxygen transport mechanisms. Therefore, our findings support this conclusion and further suggest that submaximal exercise is also limited by oxygen transport abnormalities.

Exercise limitation and ventilatory abnormalities: The other major factor that has been postulated to limit the exercise capacity of patients with heart failure is ventilatory abnormalities. Our results suggest that major abnormalities in the ventilatory response to exercise are a characteristic accompaniment of chronic cardiac failure. During both maximal and submaximal exercise, ventilatory levels were linearly related to $\dot{V}CO_2$, as in normal subjects.[12,13–15] The mean slopes of these relations were both over twice normal, indicating that more respiratory effort was expended ventilating anatomic or physiologic dead space, or both.[14] This finding is consistent with a recent preliminary report that dead space is increased during exercise in patients with chronic cardiac failure.[21] Similar ventilatory abnormalities have been described previously in patients with mitral stenosis.[22–26]

Our findings suggest, however, that these ventilatory abnormalities do not limit the exercise capacity of patients with chronic compensated heart failure. During submaximal exercise, the patients in this study usually did not report dyspnea. During maximal exercise, dy-

spnea was frequent, probably due to the development of higher levels of minute ventilation than those achieved during submaximal exercise. However, patients reported that this symptom did not cause them to terminate exercise. In support of this subjective impression, patients were invariably able to exercise to work loads that produced elevated blood lactate concentrations and marked oxygen extraction.

Moreover, the dyspnea noted during maximal exercise may actually be due to abnormal oxygen transport to working muscle. Minute ventilation characteristically increased out of proportion to oxygen uptake during the latter half of the maximal exercise protocol (Fig. 3). This disproportionate increase in minute ventilation is due to buffering of lactate by bicarbonate and consequent release of carbon dioxide.[3,8,14] If oxygen delivery to working muscle had been adequate and lactate release had not occurred, minute ventilation would have been less and dyspnea might have been markedly diminished or prevented. During submaximal exercise, minute ventilation usually did not increase out of proportion to oxygen uptake because the rate of increase in lactate was not as rapid as that during maximal exercise. Therefore, the amount of carbon dioxide released each minute by bicarbonate buffering of lactate was much lower during submaximal than during maximal exercise. Arterial hypoxemia also did not occur during either maximal or submaximal exercise, indicating that ventilatory abnormalities do not limit exercise by interfering with oxygen uptake in the lungs.

Mechanism of ventilatory abnormalities: Ventilatory abnormalities during exercise in patients with heart failure have often been attributed to acute elevations in pulmonary wedge pressure during exertion producing pulmonary congestion.[22–24] If an acute elevation in wedge pressure is the primary stimulus to excessive ventilatory patterns, the much more prolonged elevations in wedge pressure noted during submaximal exercise would be expected to produce more excessive ventilation than that produced during maximal exercise. Moreover, with progressive maximal and submaximal exercise, a progressive increase in wasted ventilation might be anticipated. We observed that ventilatory levels were linearly related to $\dot{V}CO_2$ throughout exercise and were not higher for any given $\dot{V}CO_2$ during submaximal versus maximal exercise. It appears likely that acute elevations in wedge pressure during exercise are not the primary stimulus to excessive ventilation. Alterations in respiratory function due to chronic pulmonary congestion or chronic lung damage therefore are probably the most important factor.

Clinical implications: Our data suggest that fatigue due to inadequate oxygen delivery to working muscle is the principal factor limiting the exercise capacity of patients with stable chronic left heart failure. Therefore, therapeutic efforts to improve the exercise capacity of such patients should focus primarily on altering skeletal muscle oxygen delivery during exercise. At present, relatively little information is available on the modulation of skeletal muscle flow during dynamic exercise in patients with heart failure or the effect of pharmacologic agents on oxygen delivery to working skeletal muscle. Further studies are needed in this area.

Dyspnea, however, may be an important factor limiting exercise in patients with heart failure and substantial fluid retention. In addition, dyspnea may be a hindrance to some daily activities in patients without substantial fluid retention. Patients often report that certain forms of exercise, such as climbing stairs, produce greater dyspnea than other activities. We did not examine symptomatic and metabolic responses to all types of exercise. Therefore, patients with chronic stable heart failure may be limited to some extent by dyspnea during certain daily activities. Nevertheless, our data still suggest that inadequate oxygen delivery to working muscle is the dominant limiting factor during exercise.

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Hemodynamic Effects of Dibutyryl Cyclic AMP In Congestive Heart Failure

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To evaluate the hemodynamic effects of dibutyryl cyclic AMP (DBcAMP) in congestive heart failure (CHF), right-sided cardiac catheterization was performed in 11 patients with CHF, and hemodynamic variables were investigated before and after infusion of various doses of DBcAMP at a rate of 0.025 to 0.2 mg/kg/min (mean 0.14 ± 0.077 [standard deviation]). DBcAMP reduced total systemic vascular resistance index from 3,171 ± 1,158 to 1,880 ± 554 dynes s $cm^{-5} \cdot m^2$ (mean ± standard deviation) and pulmonary arterial end-diastolic pressure from 23 ± 13 to 20 ± 11 mm Hg, and increased cardiac index from 2.24 ± 0.60 to 3.41 ± 1.02 liters/min/m^2. Mean arterial blood pressure decreased from 91 ± 14 to 84 ± 13 mm Hg, and heart rate increased from 91 ± 16 to 99 ± 13 beats/min. The increase in cardiac index was accompanied by a proportional decrease in total systemic vascular resistance index in all patients except 1. In 8 patients the decrease in pulmonary arterial end-diastolic pressure was accompanied by an increase or no change in the left ventricular stroke work index. In 6 patients, DBcAMP was given in incremental doses of 0.05, 0.1, and 0.2 mg/kg/min every 20 minutes, and 5 of 6 patients tolerated the full dose and showed dose-related hemodynamic changes for the incremental doses of DBcAMP. These data suggest that DBcAMP has powerful vasodilating effects on resistance vessels in patients with CHF; hence, it can be a useful vasodilating agent for treatment of CHF.

Since the discovery of cyclic AMP (adenosine 3′,5′-monophosphate) by Sutherland and Rall[1] in 1958, it has been found to act as a mediator in the action of various hormones. The second messenger theory has been proposed concerning the relation between catecholamine and cyclic AMP. According to this theory, the positive inotropic effects of catecholamines result from an increase in the intracellular level of cyclic AMP produced by activation of adenyl cyclase.[2–4] However, exogenous cyclic AMP does not produce such positive inotropic action because it does not penetrate the cell membrane at a rate sufficient to achieve an effective intracellular concentration.[5] However, dibutyryl cyclic AMP (DBcAMP), a derivative of cyclic AMP, is thought to penetrate the cell membrane more easily than cyclic AMP and to be resistant to inactivation by phosphodiesterase.[6]

In a variety of studies using perfused heart-lung preparations and experimental animals, it has been shown that a relatively large amount of DBcAMP has a positive inotropic effect and a positive chronotropic effect similar to that of catecholamines.[7–12] In addition, it has been reported that DBcAMP increases renal and mesenteric arterial blood flow and decreases peripheral vascular resistance.[13] No information is available on the hemodynamic responses to DBcAMP in patients with congestive heart failure (CHF). This study was designed to examine the hemodynamic effects of DBcAMP and to evaluate the clinical efficacy of this agent in patients with CHF.

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Methods

Subjects: Eleven hospitalized patients with CHF diagnosed on the basis of dyspnea, cardiomegaly, basilar rales, elevated jugular venous pressure, and signs of pulmonary hypertension were studied. Their age and sex, the cause and severity of congestive heart failure, and drugs concomitantly given are shown in Table I. Digitalis, diuretics, and nitroglycerin ointment were withheld 6 hours before each study. Various catecholamines were administered at the same doses throughout the studies.

Methods: In all patients, right pulmonary arterial and right atrial pressures were continuously monitored through a Swan-Ganz balloon-tipped triple-lumen catheter (Edwards Laboratories), 746 Simens pressure transducers, and Simens Mingograf 34. Cardiac output was measured by thermodilution techniques with the use of ice-cold water. Computation of cardiac output was performed by a bedside computer (model 9520 cardiac output computer, Edwards Laboratories). Mean arterial blood pressure (MBP) was estimated from the following formula: MBP = diastolic pressure + (systolic pressure − diastolic pressure)/3. Pulmonary arterial end-diastolic pressure was used to determine left ventricular filling pressure. The following parameters of cardiac performance were calculated: cardiac index = cardiac output/body surface

TABLE I Subjects

Case	Age (yr) & Sex	Diagnosis	Forrester's Hemodynamic Subset	Combined Drugs
1	68F	SH	. . .	None
2	57M	DC	. . .	Digitalis, diuretics
3	65M	SH	. . .	Nifedipine
4	54M	MR	. . .	Digitalis, diuretics
5	69F	SH	. . .	None
6	57M	DC	. . .	Diuretics
7	68F	AMI	H-IV	Digitalis, diuretics
8	69M	SH	. . .	None
9	68M	AMI (RV)	H-I	Dobutamine, dopamine, noradrenaline, IABP
10	69M	AMI	H-IV	Dopamine, dobutamine
11	68M	AMI	H-IV	NTG ointment, dopamine, dobutamine

AMI = acute myocardial infarction; DC = dilated cardiomyopathy; IAPB = intraaortic balloon pumping; MR = mitral regurgitation; NTG = nitroglycerin; RV = right ventricular; SH = systemic hypertension.

area (BSA) (liters/min/m^2); stroke volume index = cardiac index/heart rate (beats/min) × 1,000 (ml/beat/m^2); left ventricular stroke work index = (MBP − pulmonary arterial end-diastolic pressure) × stroke volume index × 0.0136 (g − m/m^2); total systemic vascular resistance index = (MBP − mean right atrial pressure)/cardiac index × 80 (dynes s $cm^{-5}{\cdot}m^2$); pulmonary vascular resistance index = (mPA − pulmonary arterial end-diastolic pressure)/cardiac index × 80 (dynes s $cm^{-5}{\cdot}m^2$), where mPA is mean pulmonary arterial blood pressure; and double product = arterial systolic blood pressure × heart rate.

The doses of DBcAMP and the time at which hemodynamic measurements were taken in each patient are shown in Figure 1. In cases 1 to 6, DBcAMP was infused continuously at rates of 0.05, 0.1, and 0.2 mg/kg/min. Each infusion rate was maintained for 20 minutes. Hemodynamic measurements were performed before and 20, 40, and 60 minutes after the start of the infusion and 30 and 60 minutes after terminating the infusion. In case 7, DBcAMP was infused at a rate of 0.2 mg/kg/min for 30 minutes. Hemodynamic measurements were repeated before and 10, 20, and 30 minutes after the start of the infusion, and 30 minutes after terminating the infusion. In case 8, DBcAMP was infused at a rate of 0.2 mg/kg/min for 20 minutes. Hemodynamic variables were measured before and 10 and 20 minutes after the start of the infusion, and 30 and 60 minutes after terminating the infusion. In case 9, DBcAMP was administered continuously at a rate of 0.05 mg/kg/min for 20 minutes and at a rate of 0.1 mg/kg/min for about 6 hours thereafter. Hemodynamic variables were measured before and 20 and 40 minutes after the start of the infusion. In case 10, DBcAMP was infused continuously at a rate of 0.05 mg/kg/min for the first 2 hours and 0.1 mg/kg/min for about 9 hours. Hemodynamic variables were measured before and 2, 4.5, and 10 hours after the start of the infusion. In case 11, DBcAMP was infused at a rate of 0.025 mg/kg/min for the first 30 minutes and at a rate of 0.05 mg/kg/min for about 100 minutes thereafter. Hemodynamic variables were measured before and 30 minutes after the start of the infusion. The data obtained were analyzed by Student's t test and a difference was regarded as significant at $p < 0.05$.

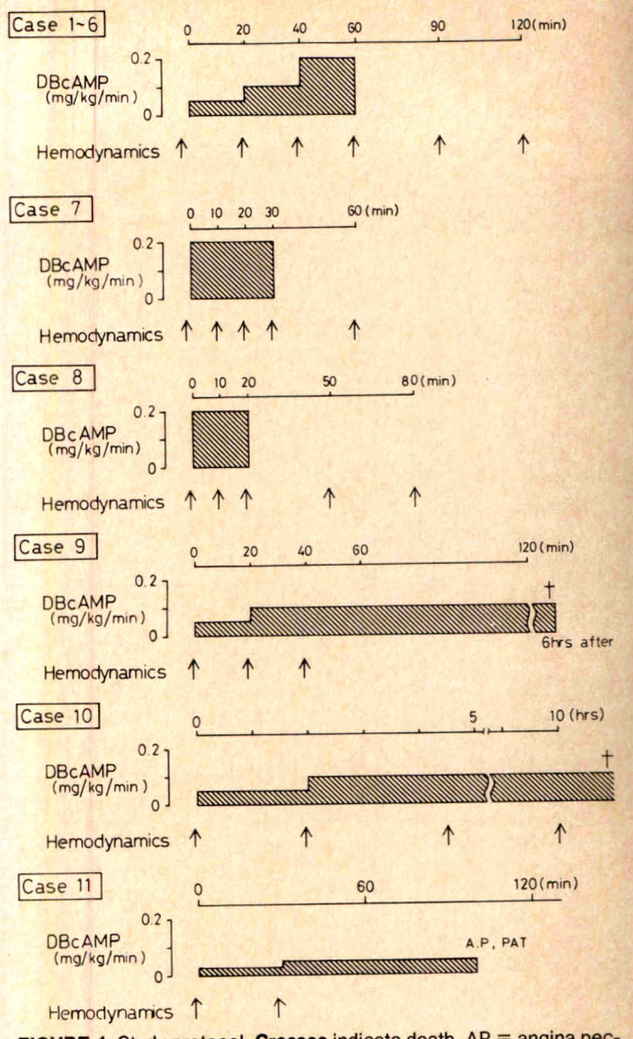

FIGURE 1. Study protocol. **Crosses** indicate death. AP = angina pectoris; PAT = paroxysmal atrial tachycardia.

Results

Hemodynamic response after intravenous administration of DBcAMP: Figure 2 shows the time course of changes of various hemodynamic variables in the patient who received continuous infusion of DBcAMP at a rate of 0.2 mg/kg/min for 30 minutes. Total systemic vascular resistance index and arterial blood pressure showed an initial decrease, whereas cardiac index showed an increase by 20 minutes and these reached constant values 20 minutes after the start of the infusion, whereas pulmonary arterial end-diastolic pressure kept declining from the beginning of the infusion to the end.

The maximal doses of DBcAMP varied from 0.025 to 0.2 mg/kg/min and averaged 0.14 ± 0.077 mg/kg/min (mean ± standard deviation). Mean arterial blood pressure, pulmonary arterial end-diastolic pressure, and total systemic vascular resistance index were significantly decreased and heart rate, cardiac index, and stroke volume index were significantly increased. However, there were no significant changes in mean

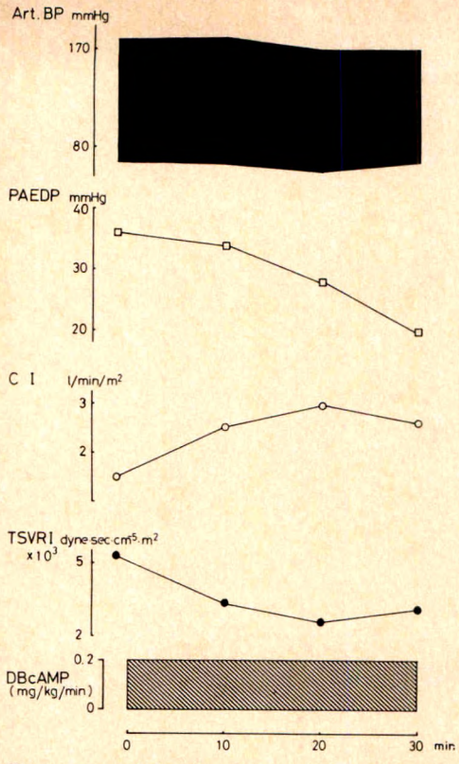

FIGURE 2. Time course of changes of various hemodynamic variables after infusion of DBcAMP in Patient 6 (age 68 years, acute myocardial infarction). Art. BP = arterial blood pressure; CI = cardiac index; PAEDP = pulmonary arterial end-diastolic pressure; TSVRI = total systemic vascular resistance index.

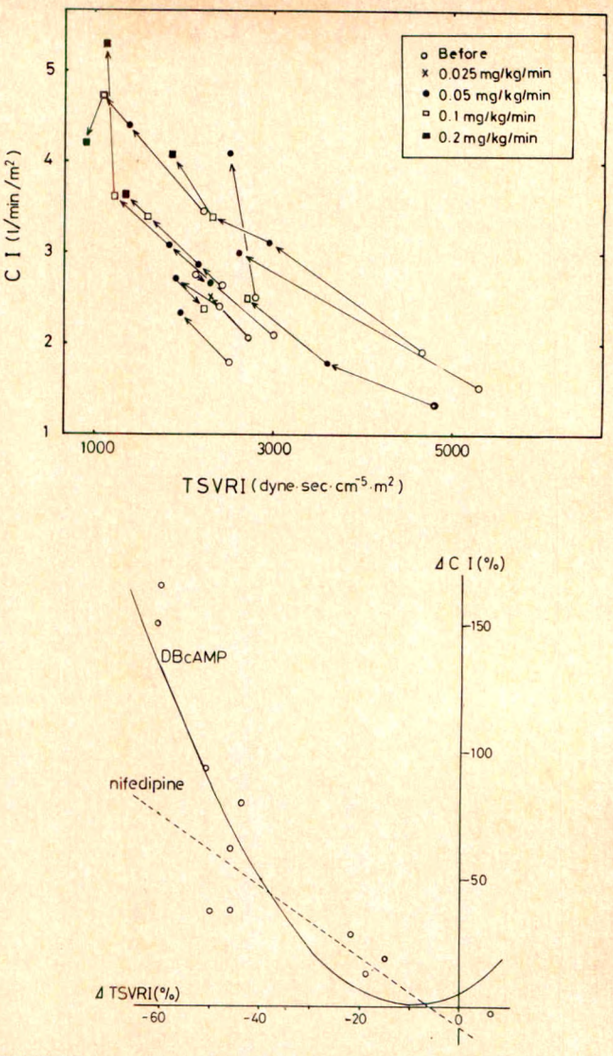

FIGURE 3. Top, effect of DBcAMP on the relation between cardiac index (CI) and total systemic vascular resistance index (TSVRI) in patients with CHF. **Bottom,** regression lines for DBcAMP and nifedipine for the percent change in cardiac index versus the percent change in the total systemic vascular resistance index. R for DBcAMP (**solid line**) = 0.90 ($p < 0.01$), R for nifedipine (**dotted line**) = 0.94 ($p < 0.01$).[14]

right atrial pressure, pulmonary vascular resistance index, and double product.

Figure 3, left, shows the change in cardiac index as a function of the changes in total systemic vascular resistance index. The increase in cardiac index was accompanied by a proportional decrease in the total systemic vascular resistance index in all patients but 1, and in 2 of them the decrease in cardiac index was accompanied by an increase or decrease in the total systemic vascular resistance index after infusing the incremental doses of DBcAMP. The relation of both parameters was regressed to a secondary degree curve with a correlation coefficient of 0.90 when their changes (cardiac index and total systemic vascular resistance index) were expressed in percentages. Compared with nifedipine,[14] DBcAMP produced larger changes in the cardiac index in patients who showed a reduction in the total systemic vascular resistance index by ≥40% (Fig. 3, right).

Individual changes in left ventricular stroke work index and pulmonary arterial end-diastolic pressure are illustrated in Figure 4. In 8 patients, the decrease in pulmonary arterial end-diastolic pressure was accompanied by an increase or no change in left ventricular stroke work index. In 2 of the other 3 patients, left ventricular stroke work index decreased together with an increase or no change in pulmonary arterial end-diastolic pressure.

In the relation between cardiac index and pulmonary arterial end-diastolic pressure, cardiac index increased along with a decrease in pulmonary arterial end-diastolic pressure in 8 of 11 patients (Fig. 5).

Dose-response relation and duration of effects: In 6 patients (cases 1 to 6), DBcAMP was given in incremental doses of 0.05, 0.1, and 0.2 mg/kg/min every 20 minutes, and 5 of 6 patients (cases 1 to 5) tolerated the full dose. DBcAMP produced a dose-related hemodynamic effect, increasing cardiac index and decreasing mean arterial blood pressure, pulmonary arterial end-diastolic pressure, and total systemic vascular resistance index. These effects of DBcAMP lasted at least 1 hour after termination of the infusion (Fig. 6).

Side effects: In case 5, arterial blood pressure decreased significantly at an infusion rate of 0.2 mg/kg/min. In case 6, premature ventricular contractions increased at an infusion rate of 0.2 mg/kg/min. In case 11, anterior chest pain and supraventricular tachycardia were noted at an infusion rate of 0.05 mg/kg/min.

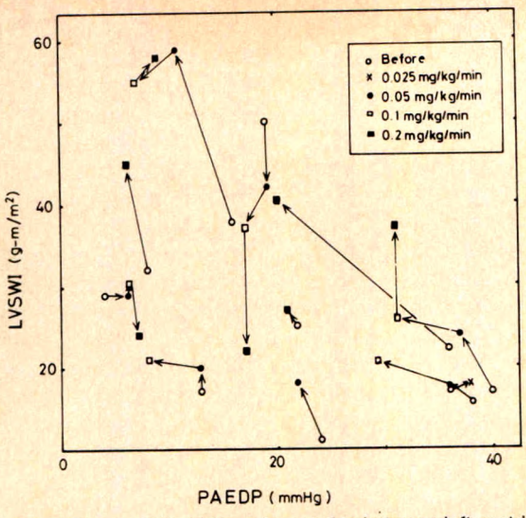

FIGURE 4. Effect of DBcAMP on the relation between left ventricular stroke work index (LVSWI) and pulmonary arterial end-diastolic pressure (PAEDP) in patients with CHF.

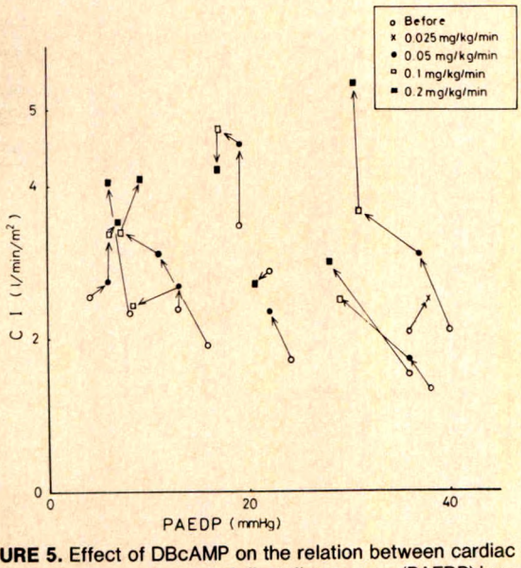

FIGURE 5. Effect of DBcAMP on the relation between cardiac index (CI) and pulmonary arterial end-diastolic pressure (PAEDP) in patients with CHF.

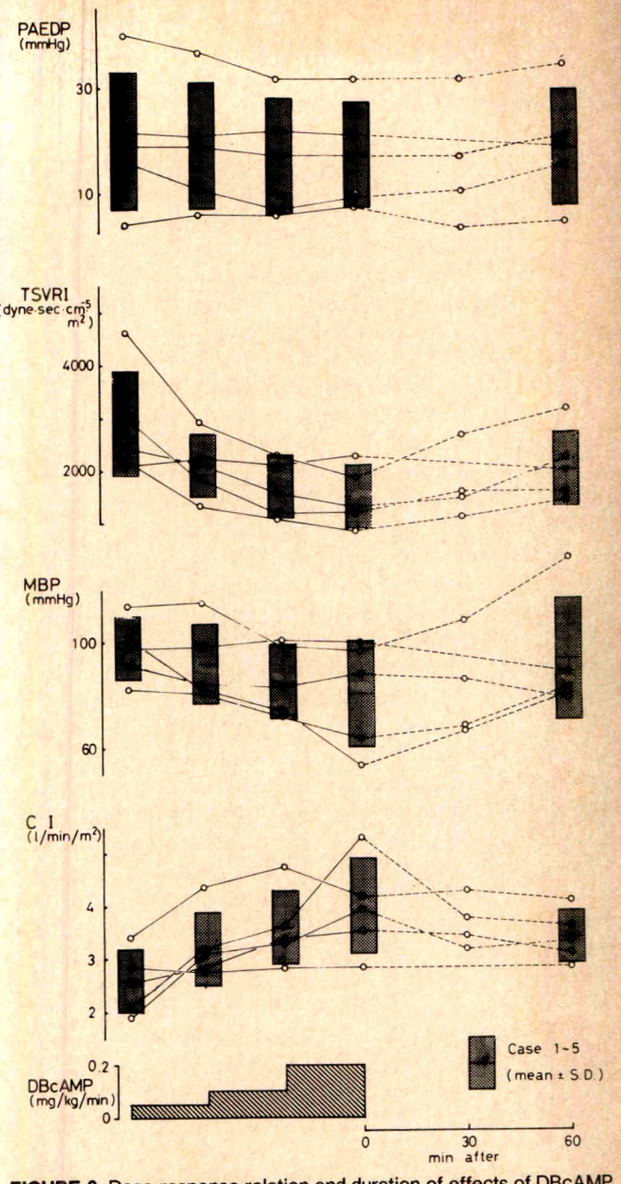

FIGURE 6. Dose-response relation and duration of effects of DBcAMP in patients with CHF (cases 1 to 5). CI = cardiac index; MBP = mean arterial blood pressure; PAEDP = pulmonary arterial end-diastolic pressure; TSVRI = total systemic vascular resistance index.

Discussion

Robinson et al[5] published the first report concerning the effects of DBcAMP on cardiac function in 1965. They reported that concentrations of DBcAMP as high as 6 by 10^{-4} *M* produced no effect on the performance of the isolated perfused rat heart. Posternak et al,[6] in anesthetized dogs, found that the intravenous injection of DBcAMP in a dose of 4 mg/kg caused only minimal and variable changes in the cardiovascular performance. However, in 1970 Kukovetz and Poch[7] reported that the addition of DBcAMP to Langendorff preparations of heart from rats, rabbits, and guinea pigs increased both their myocardial contractility and their phosphorylase activity. After this report, Skelton et al,[8] Iwatsuki and Iwatsuki,[10] and Imai et al[11] demonstrated successively that DBcAMP increased both myocardial contractility and heart rate. Nozaki and Okuaki[13] reported that the administration of DBcAMP at a dose of 5 mg/kg increased cardiac output and renal blood flow and decreased mean arterial blood pressure and total peripheral vascular resistance in anesthetized dogs. The explanation for these differences in cardiac response by DBcAMP between studies is not yet clear, but they may be related to species differences as well as to differences in dose. Thus, optimal doses of DBcAMP may have positive inotropic and chronotropic effects on the heart and vasodilating effects in the peripheral vessels. Moreover, previous studies have indicated that the positive inotropic effect of DBcAMP is not suppressed by beta-receptor blocking agents and DBcAMP may have a direct dilating effect on coronary arteries.[8,9,11,13]

A few clinical reports have described the hemodynamic effects of DBcAMP during cardiac catheterization or after extracorporeal circulation.[15–18] In these reports (in which the dose of DBcAMP was 0.2 mg/kg/min or a single injection of 5 mg/kg), a marked increase in cardiac output, a decrease in peripheral vascular resistance, and a slight increase in heart rate were observed. However, some investigators have reported that DBcAMP showed no positive inotropic effect.[18]

These results in experimental animals and the clinical studies suggest that DBcAMP may be useful in the management of CHF. However, there have been no reports concerning the effects of DBcAMP on CHF. In the present study the administration of DBcAMP at a rate of 0.025 to 0.2 mg/kg/min markedly decreased total peripheral vascular resistance and increased cardiac output in patients with CHF. Heart rate was increased slightly, arterial blood pressure was decreased, and pulmonary arterial end-diastolic pressure, indicative of left ventricular filling pressure, was decreased slightly. The double product, indicative of myocardial oxygen consumption, was not changed significantly. These results suggest that DBcAMP may be useful as a therapeutic agent for CHF.

There was no direct relation between pulmonary arterial end-diastolic pressure and cardiac index after administration of DBcAMP, as would be predicted by a simple Starling mechanism with fixed impedance and myocardial contractility. The change in cardiac output was proportional to the decrease in systemic vascular resistance by the administration of DBcAMP. Thus, the effect of DBcAMP on cardiac output is thought to be mediated in large part by a change in systemic vascular resistance. However, when a decrease in the total systemic vascular resistance index expressed as a percent of the control was reduced by more than 40%, an increase in cardiac index by DBcAMP was more than that by nifedipine, a calcium antagonist with a strong dilating effect on the resistance vessels.[14] Therefore, DBcAMP was thought to have a slight positive inotropic effect at an infusion rate of 0.025 to 0.2 mg/kg/min. Unchanged mean right atrial pressure suggests that DBcAMP has no effect on the venous bed, so that the reduction in left ventricular filling pressure is presumably due to improvement in the left ventricular pump function.

In most patients an increase in cardiac index and left ventricular stroke work index was accompanied by a decrease in left ventricular filling pressure. These results suggest that DBcAMP improved left ventricular function in patients with CHF. However, as in 2 patients, the left ventricular function was deteriorated by DBcAMP, careful hemodynamic monitoring should be performed during intravenous administration of this drug.

The maximal effect of DBcAMP on cardiac index and total systemic vascular resistance index appeared 20 minutes after initiation of the infusion and the effect lasted for at least 1 hour after termination of the infusion. The effect of DBcAMP was dose-dependent at an infusion rate from 0.05 to 0.2 mg/kg/min. However, DBcAMP at a dose of 0.2 mg/kg/min caused marked hypotension in case 5 and increased premature ventricular contractions in case 6. From these results, the most effective dose range of DBcAMP in patients with CHF appeared to be 0.05 to 0.1 mg/kg/min, but in case 11 chest pain and supraventricular tachycardia were observed at a rate of 0.05 mg/kg/min. Therefore, the administration of DBcAMP should be commenced with a smaller dose and increased gradually under careful hemodynamic monitorings.

Because DBcAMP has a powerful vasodilating effect on resistance vessels in the dose range used here, it is expected to be useful for vasodilator therapy of CHF. Moreover, DBcAMP was thought to have a slight positive inotropic effect in patients with CHF. Thus, these hemodynamic effects of DBcAMP support the clinical usefulness of this drug in the management of patients with CHF.

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Pharmacokinetic and Pharmacodynamic Effects of Diltiazem

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The pharmacokinetic and pharmacodynamic effects of diltiazem were studied in 8 patients after a short intravenous infusion (20 mg over 10 minutes), a single oral dose (60 or 90 mg), and repeated oral administration (60 or 90 mg every 6 hours for 16 doses). Diltiazem levels decreased in a triexponential manner after intravenous infusion. Terminal half-lives after intravenous, single oral, and repeated oral administration were not significantly different (4.5 ± 1.3, 3.7 ± 0.6, and 4.9 ± 0.4 hours, respectively). The kinetic effects of oral diltiazem were nonlinear. With repeated oral administration, there was accumulation of both diltiazem and its metabolite, deacetyldiltiazem. The diltiazem area under the time versus concentration curve increased by a factor of 2.39 ± 0.42 ($p = 0.00002$). Most patients showed a double peaked time versus concentration curve after oral administration, indicating possible enterohepatic recirculation.

After intravenous administration, there was a substantial increase in the P-R interval (14.3 ± 5.4%). Although only small changes in P-R interval were seen with a single oral dose, with chronic administration there was persistent P-R interval prolongation, peaking at 17.3 ± 5.6% over control. Counterclockwise hysteresis was present in the P-R interval versus plasma diltiazem concentration curve after intravenous administration. Only small changes were seen in heart rate and blood pressure.

Diltiazem hydrochloride (d-cis-3-acetoxy-2,3-dihydro-5-[2-(dimethyl-amino)-ethyl]-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride) is a new benzothiazepine derivative with cardiac and smooth muscle calcium-channel blocking activity. It is a potent vasodilator useful in the treatment of angina pectoris (due to coronary artery spasm or atherosclerosis), systemic hypertension, pulmonary hypertension, and hypertrophic cardiomyopathies.[1–5] Limited information is available about the clinical pharmacologic effects of diltiazem because the assay procedure for plasma drug levels has been cumbersome and not widely available. In this report we describe the detailed pharmacokinetic effects of oral and intravenous diltiazem measured using a new sensitive and specific high performance liquid chromatographic assay. In addition, we describe the pharmacodynamic aspects of P-R interval prolongation with diltiazem, which is a measure of its negative dromotropic effect.

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Methods

Eight patients with a history of paroxysmal atrial tachycardia (3 women and 5 men, aged 22 to 58 years) were admitted to the Duke University Clinical Research Unit. One patient had a delta wave on the electrocardiogram recorded during sinus rhythm (Wolff-Parkinson-White syndrome). Three patients had coexisting diseases: 1 each with chemical diabetes, chronic obstructive pulmonary disease, and type IV hyperlipidemia. All medications were discontinued at least 5 half-lives before admission, except in 1 patient who required continuous theophylline therapy.

All studies were performed while patients were in normal sinus rhythm. Patients were given nothing by mouth and were kept at complete bed rest from midnight forward on each study day. Between 7 and 8 A.M. a Teflon® catheter (Quick Cath 2N114, Travenol Laboratories) was inserted into a superficial forearm vein and capped with a sterile obturator (Quick Cath 2N1152, Travenol Laboratories). The catheters were kept open by the sterile obturators and heparin was not used. On days when intravenous studies were performed, a second Teflon catheter was inserted into the opposite arm and connected to a continuous infusion of 5% dextrose solution. An electrocardiographic telemetry transmitter (Hewlett-Packard model 78100A and 78101A) was used to record a

TABLE I Pharmacokinetic Effects of Intravenous Diltiazem

Patient	A (ng/ml)	α (h^{-1})	B (ng/ml)	β (h^{-1})	G (ng/ml)	γ (h^{-1})	$t^{1}/_{2}\alpha$ (h)	$t^{1}/_{2}\beta$ (h)	$t^{1}/_{2}\gamma$ (h)	AUC (h·ng/ml)	Vc (liters)	Vd_{area} (liters)	Vd_{ss} (liters)	C_{max} (ng/ml)
1	527	14.9	90	1.49	67	0.247	0.046	0.465	2.80	365	29.3	222	170	368
2	593	26.0	131	1.48	32	0.148	0.027	0.467	4.68	326	26.4	415	285	269
3	377	15.9	96	0.99	49	0.175	0.044	0.699	3.96	402	38.3	285	211	263
4	538	33.1	149	1.90	26	0.106	0.021	0.366	6.53	337	28.0	560	410	266
5*	1,208	24.9	197	1.35	53	0.119	0.028	0.512	5.84	644	13.7	261	187	598
6	332	10.3	87	1.58	34	0.156	0.068	0.438	4.44	305	44.2	420	309	348
7	333	13.4	94	1.58	32	0.220	0.052	0.438	3.15	229	43.5	397	266	251
8	718	25.8	87	1.67	37	0.165	0.027	0.415	4.19	306	23.7	396	301	288
Mean	578.3	20.5	116.4	1.51	41.3	0.167	0.039	0.475	4.45	364.3	30.9	369.5	267.4	331.4
SD	228.3	8.0	39.8	0.26	13.8	0.047	0.016	0.010	1.26	123.7	10.5	108.9	78.0	115.8

* Patient 5 received 17 mg and all dose-dependent variables were extrapolated to 20 mg.

A, B, and G are the time-zero intercepts and α, β, and γ the rate constants for the triexponential equation $Ct = Ae^{-\alpha t} + Be^{-\beta t} + Ge^{-\gamma t}$ used to describe the decrease in plasma concentration after intravenous injection. Ct is the concentration of drug at time = t. $t^{1}/_{2}\alpha$, $t^{1}/_{2}\beta$, and $t^{1}/_{2}\gamma$ are the half-lives for the α, β, and γ phases of drug elimination. AUC is area under the plasma concentration versus time curve. Vc is the volume of the central compartment calculated using the equation: Vc = dose/(A + B + G). Vd area is the volume of distribution calculated using the equation: Vd_{area} = dose/(AUC × γ). Vd_{ss} is volume of distribution at steady-state. C_{max} is the maximum plasma level of diltiazem after the intravenous infusion.

modified electrocardiographic lead II (right shoulder negative, cardiac apex positive). The electrocardiogram was displayed continuously on an oscilloscope and recorded on an Elema Mingograph model 1600 ink-jet recorder. Between 8 and 9 A.M., electrocardiogram rhythm strips that included at least 10 consecutive sinus beats were recorded at a paper speed of 100 mm/s, and blood pressure was measured by a sphygmomanometer at 15-minute intervals. At exactly 9 A.M. the medication was given. For intravenous administration, 20 mg of diltiazem (Cardizem, Marion Laboratories) in a solution of 1 mg/ml of sterile water was given over 10 minutes by constant infusion pump (Harvard Apparatus infusion withdrawal pump). Blood samples were obtained before the infusion began and at t = 0, 2, 3, 5, 7, 10, 15, 30, 45, and 60 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after completion of the infusion. Blood pressure was measured and electrocardiogram rhythm strips were recorded at the time each blood sample was drawn.

Two days after the intravenous infusion study, a single oral dose of diltiazem was given (60 or 90 mg as two or three 30 mg tablets of the Tanabe formulation). Blood samples were obtained, electrocardiographic rhythm strips were recorded, and blood pressure was measured immediately before the tablets were given and at t = 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, and 12 hours after the dose was given. After the 12-hour sample was obtained, patients were given oral diltiazem every 6 hours, continuing the dose they received for the initial oral study (60 mg for the first 4 patients and 90 mg for the last 4 patients). Blood samples were obtained each morning at 9 A.M. to determine trough plasma diltiazem levels. Four days after the single-dose study, a repeat pharmacokinetic study was done over the same 12-hour period to assess steady-state pharmacokinetic effects after the 16th dose.

Blood samples were drawn into plastic syringes and immediately transferred to silanized glass tubes with 10 U/ml of heparin. Plasma was separated and frozen at −20°C and later analyzed for diltiazem and deacetyldiltiazem using a high performance liquid chromatographic method described by Verghese et al.[6] The mean P-R interval and cardiac cycle on 10 consecutive heart beats recorded at the specified sampling times were measured using an interactive computer program, except for the patient with the Wolff-Parkinson-White syndrome who was excluded from analysis of electrocardiographic data. Electrocardiograms were measured and blood samples assayed blindly by personnel in separate laboratories.

Initial estimates of the intravenous parameters were obtained using linear regression of time versus log of concentration plots. These estimates were refined by nonlinear regression analysis for both a 2 and a 3 exponential model. Half-lives ($t^{1}/_{2}$) for the oral studies were determined using linear regression of the terminal portion of the time versus concentration curves. The area under the time versus concentration curve (AUC) was estimated by the trapezoid rule. The accumulation factor (A) was calculated using the following equation: $A = AUC_{16}0 \rightarrow 6/AUC_{1}0 \rightarrow \infty$ where $AUC_{16}0 \rightarrow 6$ is the AUC after the 16th oral dose from 0 to 6 hours, and $AUC_{1}O \rightarrow \infty$ is the AUC after the first oral dose extrapolated to infinity. The apparent bioavailability (F), was calculated using the equation: $F = (AUC_{oral}/AUC_{iv}) \times (D_{iv}/D_{oral})$, where D_{iv} is the intravenous dose and D_{oral} the oral dose given. Volume of distribution at steady state (Vd_{ss}) was calculated using the equation: $Vd_{ss} = [(A/\alpha^2 + B/\beta^2 + G/\gamma^2)/(AUC_{iv}0 \rightarrow \infty)] \times$ clearance. The half-lives of the intravenous, the first oral, and the steady-state oral studies were compared using the analysis of variance. Other comparisons were analyzed using the paired *t* test.

Patient 5 received only 17 mg during the intravenous study because the infusion rate was inappropriately slow. Plasma

levels and all dose-dependent parameters were extrapolated to a dose of 20 mg in this patient.

Results

Pharmacokinetic effects: Immediately after the short intravenous infusion plasma levels peaked at 312 ± 93 ng/ml and thereafter decreased triexponentially (Table I, Fig. 1). The mean terminal half-life was 4.5 ± 1.3 hours. Plasma diltiazem was not detectable after 24 hours except in 2 patients, and they had only a trace amount. Deacetyldiltiazem was measured in all 8 patients at t = 0 after the infusion (peak plasma level 41.1 ± 19 ng/ml), but plasma levels of the metabolite were not adequate to determine its kinetic effects.

There was substantial overlap in the results obtained with the 60 and 90 mg single oral doses; combined results are presented in Table II. In 6 of 8 patients we found 2 distinct plasma diltiazem peaks, 63.0 ± 34 ng/ml at 1.8 ± 0.5 hours and 64.7 ± 39 ng/ml at 4.7 ± 0.7 hours (Fig. 2). The peak plasma diltiazem levels in the remaining 2 patients were 92 ng/ml at 4.5 hours and 61 ng/ml at 4.5 hours. The mean terminal half-life after the later peak was 3.7 ± 0.6 hours, not significantly different from that found after intravenous administration (described earlier) or after steady-state oral dosing (described later).

Deacetyldiltiazem was not detected in 1 patient receiving a 60 mg dose and in 1 patient receiving a 90 mg dose. In the other 6 patients, peak levels ranged from 6 to 27 ng/ml (20 ± 7.7). As after intravenous diltiazem, deacetyldiltiazem levels after a single oral dose were not high enough to determine its kinetics. In addition, there was considerable fluctuation in the metabolite level from hour to hour, making it impossible to measure rate constants.

During chronic administration, trough plasma levels increased initially and then stabilized after 48 hours (7 doses), indicating that steady-state plasma drug levels had been achieved. After the 16th dose, 4 patients continued to have 2 diltiazem peaks in plasma: 205 ± 80 ng/ml at 1.6 ± 0.6 hours and 192.5 ± 79 ng/ml at 4.0 ± 1.0 hours. The 4 patients with single peaks achieved levels of 144 ng/ml at 1.5 hours, 473 ng/ml at 2.0 hours, 277 ng/ml at 2.5 hours, and 361 ng/ml at 4.5 hours. The mean terminal half-life of diltiazem was 4.9 ± 0.4 hours at steady-state.

The mean peak plasma deacetyldiltiazem level after the 16th dose was 93 ± 76 ng/ml. In 6 patients, the deacetyldiltiazem level peaked 1 to 5 hours after dosing (Fig. 3A). The terminal half-life was 6.1 ± 1.2 hours in 5 patients for whom this calculation could be made. In 2 patients, the plasma deacetyldiltiazem level showed no decrease during the 12-hour study interval, and levels were higher than diltiazem in 1 patient (Fig. 3B). This latter patient required continuous theophylline therapy throughout the study, and the relation to deacetyldiltiazem levels is not clear.

When steady-state was achieved, the AUC had significantly increased from 505 ± 205 ng/ml × hour after the initial dose to 1,216 ± 562 ng/ml × hour (p = 0.0008). The mean accumulation ratio was 2.39 ± 0.42. In addition, the apparent bioavailability increased from 38 ± 11% to 90 ± 21% (p = 0.00002). In 3 patients the apparent bioavailability was >100% after the 16th dose.

Pharmacodynamic effects: The mean P-R intervals recorded during control periods were 161 ± 11 ms on the intravenous dosing day and 159 ± 12 ms on the first oral dosing day (p = 0.4). After intravenous diltiazem, the P-R interval increased by 14.3 ± 5.4%. Peak prolongation occurred 11.4 ± 2.4 minutes after the infusion

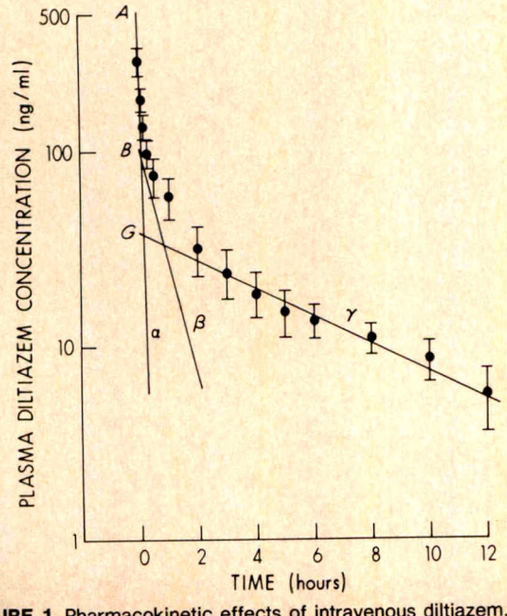

FIGURE 1. Pharmacokinetic effects of intravenous diltiazem. Mean diltiazem plasma levels (± standard deviation) in 7 patients after a 20 mg infusion. See Table I for an explanation of abbreviations.

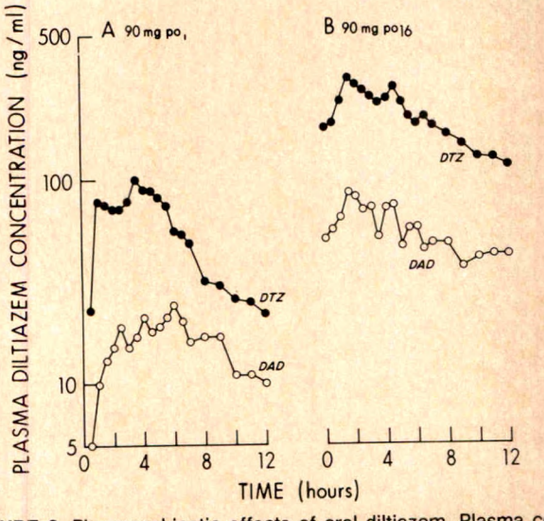

FIGURE 2. Pharmacokinetic effects of oral diltiazem. Plasma concentration curve of diltiazem (DTZ) and deacetyldiltiazem (DAD) after the first (**A**) and 16th doses (**B**) in a patient given 90 mg of diltiazem orally. In both studies this patient had the characteristic secondary diltiazem peak.

TABLE II Pharmacokinetic Effects of Oral Diltiazem

Patient	Dose (mg)	AUC1 (h·ng/ml)	AUC16 (h·ng/ml)	$t_{1/2}-1$ (h)	$t_{1/2}-16$ (h)	F1	F16	A	$C_{max}1$	$C_{max}16$	Weight (kg)
1	60	511	1,188	3.09	4.50	0.47	1.08	2.32	92	361	102
2	60	301	646	4.74	4.44	0.31	0.66	2.15	29	128	90
3	60	729	1,455	3.55	6.54	0.60	1.21	2.00	101	308	83
4	60	373	741	4.34	3.00	0.37	0.73	1.98	40	171	75
5	90	880	2,320	3.33	4.56	0.30	0.87	2.64	126	473	54
6	90	472	1,539	4.02	5.73	0.34	1.12	3.26	61	277	76
7	90	303	688	3.51	4.67	0.29	0.67	2.27	55	144	116
8	90	470	1,154	3.33	5.33	0.34	0.84	2.46	60	246	74
Mean		504.9	1,216.4	3.74	4.85	0.38	0.90	2.39	70.5	263.5	...
SD		204.6	562.4	0.57	1.05	0.11	0.21	0.42	32.9	117.8	...

A = accumulation factor; AUC = area under concentration versus time curve; C_{max} = maximum concentration; F = bioavailability; $t_{1/2}$ = half-life.

stopped and thus lagged behind the peak plasma diltiazem level. This lag caused counterclockwise hysteresis in the curve of P-R interval prolongation versus plasma diltiazem concentration (Fig. 4). After the first oral dose, P-R interval prolongation was only 6.0 ± 1.5% for 4 patients receiving 60 mg and 8.0 ± 3.6% for patients receiving 90 mg. These changes were too small to determine whether hysteresis was present.

When diltiazem was given to steady-state, P-R interval prolongation persisted throughout the dosing interval. The P-R interval at the time the 16th dose was given was 176 ± 17.6 ms or 10.6% greater than that recorded during the control period of the first oral dosing day ($p = 0.002$). The peak P-R interval after the 16th dose was 187.4 ± 16.7 ms or 17.3% greater than that recorded during the control period of the first oral dosing day, and occurred 1.5 ± 0.05 hours after the dose. Six hours after the 16th dose, the P-R interval was still significantly prolonged at 171.3 ± 13.5 ms ($p = 0.003$).

There was no clinically important change in heart rate recorded on any study day. On the intravenous dosing day, the mean heart rate was 66.6 ± 15 beats/min during the control period and 71.5 ± 13 beats/min at the end of infusion. Blood pressure decrease was modest during intravenous dosing. In most patients the maximum decrease in blood pressure occurred at the end of the intravenous infusion. The average decrease was 6.3 mm Hg in systolic and 4.0 mm Hg in diastolic blood pressure between control values and values immediately after infusion. Changes in blood pressure were even less in the oral dosing studies.

No significant adverse effects occurred which could be attributed to diltiazem. No patient had clinically important hypotension, or changes in blood counts, renal function, electrolytes, or liver function test results.

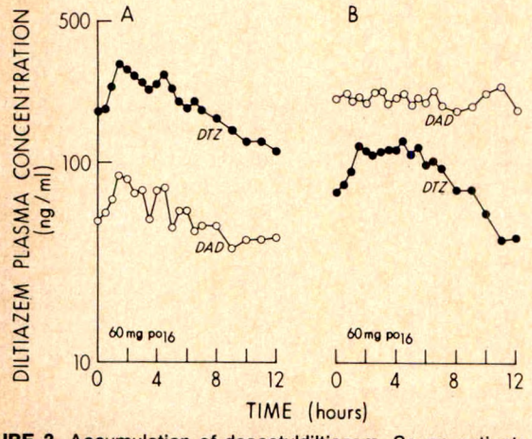

FIGURE 3. Accumulation of deacetyldiltiazem. Seven patients had plasma deacetyldiltiazem (DAD) levels lower than plasma diltiazem (DTZ) levels at steady-state (**A**). In 1 patient, plasma deacetyldiltiazem levels exceeded those of the parent compound (**B**).

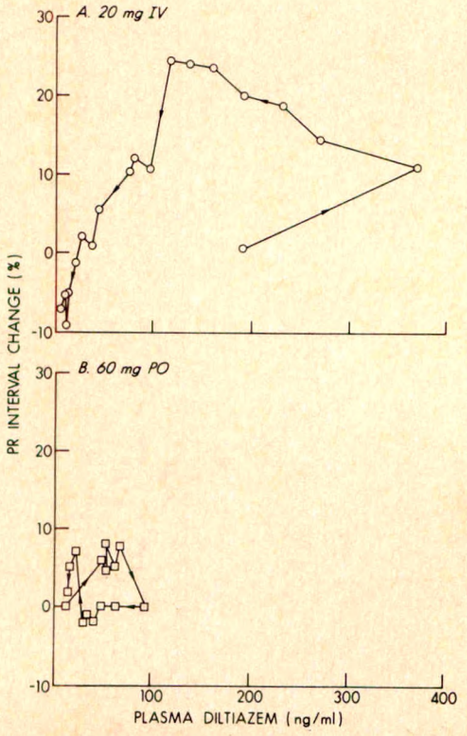

FIGURE 4. Percent change in P-R interval from control versus plasma diltiazem concentration after intravenous (IV) (**A**) and oral (PO) (**B**) diltiazem. Counterclockwise hysteresis was present after intravenous administration.

Discussion

Diltiazem is a new calcium-channel blocking drug that probably will soon be widely used for the treatment of angina. Important new findings in our study are (1) nonlinear kinetic effects leading to a significant accumulation with chronic oral dosing, (2) substantial levels of deacetyldiltiazem (exceeding those of the parent compound in some patients) that might contribute to therapeutic or toxic effects, (3) double peak in plasma drug concentration versus time curve consistent with enterohepatic recirculation, (4) sustained atrioventricular nodal slowing measured as P-R interval prolongation with chronic dosing, (5) terminal half-life 4.5 hours and triexponential elimination after intravenous administration, and (6) counterclockwise hysteresis in P-R interval versus plasma drug concentration curves after rapid infusion.

Oyama et al[7] previously reported a half-life of 2 hours for intravenous diltiazem, which is substantially shorter than our value of 4.5 hours. This discrepancy may be explained because Oyama et al used a 2-compartment model to describe their data. In the present study, diltiazem elimination was clearly triexponential in all patients. Our values for the half-life after first oral and steady-state oral dosing (3.7 and 4.9 hours, respectively) are more consistent with those previously reported for single oral doses.[8–10] In contrast to verapamil, which has a half-life that increases with chronic oral dosing, we found that diltiazem's half-life was not affected by route of administration or length of treatment.[11] Like those of verapamil, our pharmacokinetic data are consistent with high "first-pass elimination" in the liver with nonlinear kinetic effects that cause unexpected drug accumulation during chronic administration. Therefore, bioavailability was low with the first oral dose (38%) but high (90%) with steady-state oral dosing. This finding differs from the findings of Rovei et al,[8] who reported only slight accumulation, and Morselli et al[9] who reported plasma drug level actually decreasing over time in some patients. The reason for this discrepancy is not obvious since we saw ≥100% increase in the AUC (or ≥50% reduction in clearance) in each patient studied. The importance of this finding is clear: like verapamil and propranolol, diltiazem given on a long-term basis leads to unexpected accumulation.[11,12] This now appears to be the rule rather than the exception for drugs with high first-pass metabolism; this is presumably due to saturation of the elimination pathway for diltiazem. This mechanism is also suggested by previous work showing a nonlinear increase in AUC with increasing dose and higher bioavailability with larger doses.[10,13] The increase we found in apparent bioavailability with time also suggests saturation.

The double peak in plasma concentration-time curves after oral administration is a new and unusual finding, but not entirely unexpected. While diltiazem is rapidly and almost completely absorbed, its main route of excretion is in the feces.[14] Using radiolabeled diltiazem, Sakuma et al[15] showed excretion into the stomach from fundic glands and into the small intestines from the bile ducts. Meshi et al[14] also showed enterohepatic recirculation using a cross-cannulation experiment in rats. Piepho et al[13] reported that 3 of 6 dogs given oral diltiazem also had secondary peaks. While this could be explained by conversion of deacetyldiltiazem back to diltiazem or the presence of an immediate and delayed release of diltiazem from the tablets, recirculation seems more likely. The finding of >100% bioavailability in 3 patients is probably due to a combination of a small amount of enterohepatic recirculation amplified by a reduction in clearance with long-term therapy.

The metabolite deacetyldiltiazem also accumulated with time in all patients, and had an elimination half-life considerably longer than its parent compound. We also found that the plasma level of the metabolite exceeded the level of diltiazem during long-term therapy in some patients. A considerably longer period of time may be required to reach steady-state levels of deacetyldiltiazem. Potential therapeutic benefits or toxic effects of deacetyldiltiazem are not known.

Although diltiazem is being introduced as an antianginal agent, it also slows atrioventricular nodal conduction (negative dromotropic effect) like verapamil. The 14% P-R interval prolongation that we found with our short infusion (20 mg over 10 minutes) is less than the 25% prolongation reported with intravenous verapamil (10 mg over 2 minutes) by Reiter et al.[16] As with verapamil, peak P-R interval prolongation occurred 11 minutes after peak plasma drug levels, causing counterclockwise hysteresis (Fig. 4), which has been reported previously only for verapamil among the calcium-channel blocking drugs.[17–19] This phenomenon is probably due to a delay in the transfer of diltiazem from the plasma to the tissue compartment, estimated by Kohno et al[20] to take 11 minutes in dogs. Counterclockwise hysteresis was also found after single oral dosing with verapamil, but with diltiazem, P-R interval prolongation and plasma levels were insufficient to assess hysteresis after a single oral dose. However, with long-term administration, as diltiazem accumulated, the P-R interval was significantly prolonged. This suggests that diltiazem will be useful in the chronic management of supraventricular tachycardias.

Diltiazem users should be aware of its unique pharmacokinetic properties. Significant accumulation occurs when the drug is given orally, which may enhance its therapeutic benefits or may possibly increase toxicity. The role of deacetyldiltiazem in the efficacy of diltiazem is uncertain, but it is present in substantial quantities. In addition, the negative dromotropic effect of both intravenous and oral diltiazem suggests that it may be useful in the treatment of supraventricular tachycardias.

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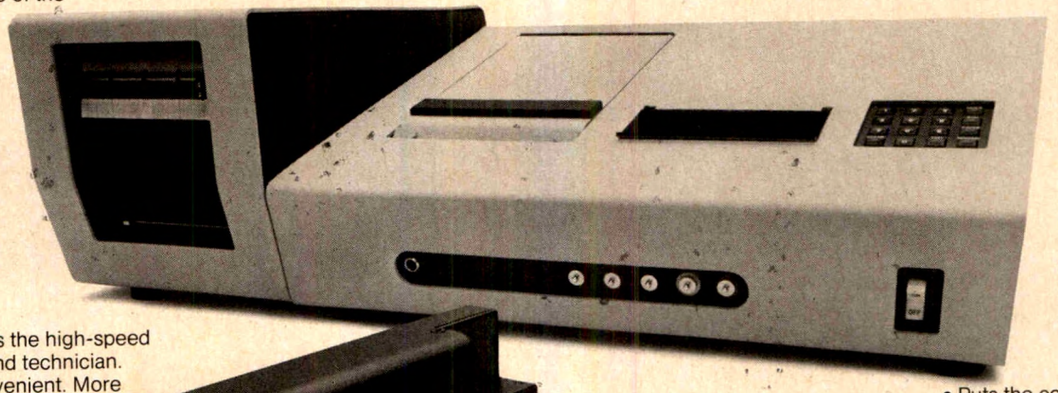

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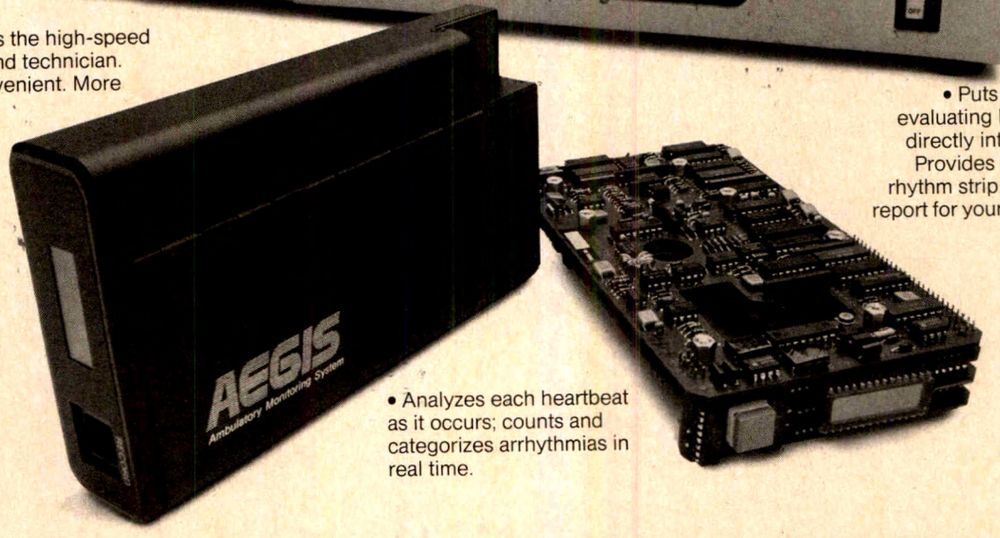

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Prevalence of Submitral (Anular) Calcium and Its Correlates in a General Population-Based Sample (The Framingham Study)

DANIEL D. SAVAGE, MD, PhD, ROBERT J. GARRISON, MS, WILLIAM P. CASTELLI, MD, PATRICIA M. McNAMARA, BA, SANDRA J. ANDERSON, BS, RN, WILLIAM B. KANNEL, MD, MPH, and MANNING FEINLEIB, MD, Dr PH

To obtain epidemiologic information on submitral calcium, 2,069 subjects in the original Framingham Study cohort (mean age 70 ± 7 years) and 3,625 of the offspring of the cohort and their spouses (mean age 44 ± 10 years) with adequate echocardiograms were evaluated. Submitral calcium was detected in 162 (2.8%) of the 5,694 subjects; >90% of the subjects with such calcium came from the 40% of the study group >59 years of age. Women were more than twice as likely to have such calcium as men. Age in both sexes, systolic blood pressure in men, and obesity in women were significantly and independently associated with submitral calcium. There was a 12-fold excess of atrial fibrillation in subjects with (20 of 162, 12%) compared with those without (53 of 5,532, 1%) submitral calcium.

Although reports of the clinical consequences of submitral calcium date back to the early 1900s, relatively scant attention has been given to this pathologic finding until recently. Increased use of echocardiography has helped rekindle interest in such calcium not only because it is often found on routine echocardiography, but also because it can be confused with other echocardiographic findings such as mitral stenosis and pericardial effusion.[1,2] D'Cruz et al[3] have suggested that echo-dense bands posterior to the anterior mitral leaflet (previously called mitral anular calcium) should be called posterior submitral calcium, because this pattern often represents calcium in the posterior submitral angle (between the posterior leaflet and left ventricular [LV] wall and not necessarily the anulus). Some reports have suggested that such calcium may be an important cause of mitral regurgitation and other types of cardiac dysfunction such as dysrhythmias.[4–7] Clinical reports have usually not included control groups to help ascertain whether findings associated with submitral calcium were simply due to the fact that most subjects with such calcium are elderly and thus are more likely to have various disorders.

Despite the potential importance of this apparently common problem, virtually no epidemiologic information is available regarding it. Routine echocardiography used in the prospective Framingham Study has permitted prevalence estimates and assessment of associations of submitral calcium in a population-based sample.

Methods

Study population: At the time of this report, 2,291 of the original Framingham cohort (biennial examination 16) and 3,664 offspring (examination 2) of the original cohort (and offspring spouses) had been studied by M-mode echocardiography. Detailed accounts of the sampling procedure for these populations and the clinical methods employed have been reported elsewhere.[8–10] Echocardiograms of adequate quality to assess the presence or absence of submitral calcium were obtained in 1,250 women and 819 men in the cohort group (mean age 70 ± 7 years [standard deviation], range 59 to 90). Such echocardiograms were obtained in 1,869 women and 1,756 men in the offspring-spouse group (mean age 44 ± 10 years, range 17 to 77). Quetelet's index (weight in kilograms

From the Framingham Heart Study, Epidemiology and Biometry Program, the National Heart, Lung, and Blood Institute, Framingham, Massachusetts; the Biometrics Research Branch, Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and Evans Research Foundation, Boston University School of Medicine, Boston, Massachusetts. This study was supported in part by contracts N01-HV-92922 and N01-HV-52971 from the National Institutes of Health, Bethesda, Maryland. Manuscript received December 15, 1982; revised manuscript received January 24, 1983, accepted January 26, 1983.

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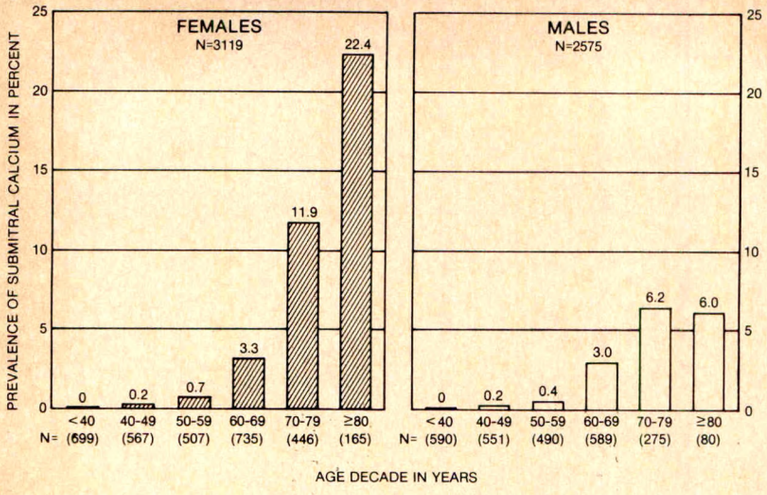

FIGURE 1. Prevalence of submitral calcium in Framingham subjects by age and sex.

divided by height in meters raised to the second power) was used as a measure of obesity. Evidence of overt cardiac disease was considered present if there were Framingham criteria for coronary disease, congestive heart failure, hypertensive heart disease, valvular heart disease (such as rheumatic heart disease), or miscellaneous "other" heart disease (such as cardiomyopathy).[10]

Echocardiographic methods: M-mode echocardiograms were performed with the subject in the partial left lateral decubitus position with the head of the bed elevated 30°. Standard techniques were employed with the transducer preferentially in the fourth intercostal space parasternally.[11] Spatial orientation was aided by the use of 2-dimensional (2-D) echocardiography in >90% of studies.

Recordings were made using an Aerotech 2.25 MHz focused transducer, a Hoffrel 201 echocardiograph interfaced with a Honeywell 1856 line scan recorder, and a Jason thermographic printer. A Hoffrel mechanical sector scanner was used for the 2-D echocardiograms. The criterion for posterior submitral calcium was the presence of an echo-dense band located immediately behind the posterior mitral leaflet (and often obscuring it). This band usually showed less motion than the endocardium of the LV posterior wall. LV wall thickness, LV internal dimensions, and left atrial dimension were measured using previously described echocardiographic methods.[12] Such measures were considered abnormal if they were greater than the published 95% confidence limits adjusted for age and body size.[12]

Statistical analyses: Where appropriate, Student's *t* test, the chi-square test, or Fisher's exact test were used to assess statistical significance. To assess the relation of submitral calcium to known risk factors for cardiac disease, univariate and multivariate logistic regression analyses were used. The regression analyses were performed using a maximum likelihood estimation and testing procedure described by Walker and Duncan.[13] Each estimated regression coefficient was tested against the alternate hypothesis that a particular partial coefficient was zero. A test outcome indicated whether the independent variable in question made a statistically significant contribution to the prediction of the dependent variable.

The dependent variable used in the multivariate analyses was the presence of posterior submitral calcium, while the independent variables were age, Quetelet's index, systolic blood pressure, blood sugar, cigarette use, and serum high- and low-density lipoprotein cholesterol levels. These independent variables, except for age, which was current, were measured 8 years before echocardiography was performed.

Results

Prevalence and association with known cardiovascular risk factors: Posterior submitral calcium was found in 162 (2.8%) of the 5,694 subjects (Fig. 1). Of the subjects with such calcium, 95% came from the 40% of the study group aged >59 years. No subject aged <45 years had submitral calcium. Women were more than twice (119 of 3,119, or 3.8%) as likely to have such calcium as men (43 of 2,575, or 1.7%), but the excess only became significant at >70 years of age when the prevalence became substantial (Fig. 1). Cardiovascular risk factors in subjects with and without submitral calcium are compared in Table I. The results of multivariate analysis to assess the independent correlates of submitral calcium are summarized in Table II.

Echocardiographic associations: Subjects with submitral calcium were significantly more likely to have increased LV wall thickness (3-fold excess), LV dilatation (2-fold excess), left atrial enlargement (3-fold excess), aortic valve calcium (5-fold excess), and reduced aortic valve leaflet motion (4-fold excess) by echocardiography. These findings remained true for age- and body size-adjusted and sex-specific comparisons of subjects with and without submitral calcium.

Only 1 of the 289 subjects with mitral valve prolapse had submitral calcium. None of the 5 subjects with prosthetic mitral valves had submitral calcium.

Associations with heart murmurs, dysrhythmias, and conduction abnormalities: The significant associations of submitral calcium with heart murmurs and atrial fibrillation (AF) are summarized in Table III. Age-decade and sex-specific comparisons indicated a 3- to 16-fold greater occurrence of submitral calcium in subjects with AF. Four of the 12 subjects with AF who had no overt evidence of cardiac or systemic disease (that is, "lone AF") had submitral calcium determined by echocardiography. Prolonged P-R intervals (>0.20 second), atrioventricular (second- or third-degree) block, bundle branch block, and artificial pacemakers

TABLE I Cardiovascular Risk Factors in Framingham Cohort Subjects With and Without Submitral Calcium

Parameter	Men				Women			
	Average Cases (n = 26)	SD	Average Noncases (n = 623)	SD	Average Cases (n = 69)	SD	Average Noncases (n = 847)	SD
Age (Yr)	73*	7	70	7	77†	7	70	7
Systolic blood pressure (mm Hg)	152‡	20	139	20	150‡	20	139	22
Quetelet's index (kg/m^2)	28	3	27	3	28‡	5	26	4
Cigarette use (%)	15	. . .	26	. . .	12*	. . .	29	. . .
Blood sugar (mg/100 ml)	121	29	114	32	117§	36	109	26
LDL cholesterol (mg/100 ml)	142	40	142	37	165§	43	155	39
HDL cholesterol (mg/100 ml)	47	12	46	13	56	17	59	16

Cases significantly different from noncases: * $p < 0.01$; † $p < 0.0001$; ‡ $p < 0.001$; § $p < 0.05$.
SD = standard deviation.

TABLE II Multivariate Logistic Regression Standardized Coefficients of Cardiovascular Risk Factors in Framingham Cohort Subjects With and Without Submitral Calcium

Parameter	Regression Coefficients	
	Men (n = 649)	Women (n = 916)
Age (yr)	0.42*	0.80†
Systolic blood pressure (mm Hg)	0.50‡	0.10
Quetelet's index (kg/m^2)	0.20	0.41‡
Cigarette use (%)	−0.14	0.14
Blood sugar (mg/100 ml)	0.08	0.10
LDL cholesterol (mg/100 ml)	0.00	0.18
HDL cholesterol (mg/100 ml)	0.05	0.06

* $p < 0.05$.
† $p < 0.0001$.
‡ $p < 0.01$.

TABLE III Frequency of Atrial Fibrillation and Heart Murmurs in Framingham Cohort Subjects With and Without Submitral Calcium

Finding	Percent of Subjects With Submitral Calcium Who Had the Finding*	Percent of Subjects Without Submitral Calcium Who Had the Finding
AF	12 (20)†	1 (53)
Systolic murmurs		
Apical holosystolic	12 (16)†	4 (69)
Basilar crescendo-decrescendo	29 (38)†	8 (150)
≥Grade 3	37 (43)‡	26 (115)
Diastolic murmurs		
Apical (mitral)	1.5 (2)§	0.4 (7)
Left sternal border (aortic)	3 (4)‡	0.6 (11)

* Numbers in parentheses represent absolute numbers of subjects with each finding. Associations of the findings with submitral calcium remained true for age- and sex-specific comparisons.
† $p < 0.0001$.
‡ $p < 0.01$.
§ $p < 0.07$.
AF = atrial fibrillation.

were no more common in subjects with than in those without submitral calcium.

Discussion

This report documents a steep age-dependent gradient of prevalence of submitral calcium in a free-living population-based sample. This is consistent with clinical reports which have only rarely reported submitral calcium in subjects under age 50.[4,14–17] The 2-fold excess of submitral calcium in women versus men in the current report is also similar to that reported in clinical studies.[4,16,17] This excess in women is not simply due to women living longer than the men since age-decade specific comparisons in the present study also show this excess.

Some controversy exists regarding whether the echo-dense band behind the posterior mitral leaflet always represents calcium.[4] Joyner et al[18] have demonstrated good correlation of the echocardiographic findings with surgery and necropsy findings of calcium even when there was no radiographically demonstrable calcium. Gabor et al[2] found excellent correlation between echocardiographic and fluoroscopic findings using an image intensifier.

The association of submitral calcium with systemic arterial hypertension in the present study has also been noted in clinical studies.[2,4,16,19,20] Systemic hypertension and aortic stenosis (evidence of which was also prominent in the present study) are both associated with increased LV systolic pressure. This increased pressure might be expected to cause increased stress to be transferred to the mitral anulus by way of the mitral valve leaflets, as outlined by Fulkerson et al.[4]

The association of submitral calcium with systolic murmurs is likely to be the result of multiple factors. First, the association with systolic ejection murmurs (especially at the base and in conjunction with aortic valvular calcium and decreased leaflet motion by echocardiography) suggests a link with aortic valvular stenosis. This association has been found in reported

linical[2,4] and autopsy[15,16] series. Alternatively, aortic alve calcium and submitral calcium may occur in arallel as part of a generalized degenerative process ith neither necessarily predisposing in a causal way to he other.

The association of submitral calcium with systolic murmurs believed to be mitral in origin suggests another actor which may accelerate such calcium. Abnormal or ncreased mitral valve motion may result in anular tresses and accelerate degenerative changes there.[4] In heir clinical series of 80 subjects with submitral calcium, the average age of 11 subjects who also had mitral alve prolapse was >10 years less than the age of those ithout prolapse (64 versus 75 years).[4] Bulkley et al[21] ound that in patients with caged-ball mitral valve replacement, progressive submitral calcification could levelop within 44 months of mitral valve replacement.

Another explanation for mitral murmurs associated ith submitral calcium in the present study is that these murmurs may have been caused by the submitral calcium. Pomerance[19] found that systolic murmurs were times more common when severe submitral calcium listorted the posterior mitral cusps than when submiral calcium was slight or moderate and without mitral alve distortion. In another report, Pomerance[22] reorted postmortem findings in 173 patients >70 years ho had systolic murmurs. Seventy patients (41%) had ubmitral calcium as the sole or predominant cardiac esion.

Although several reports[2,4,23,24] of submitral calcium ave prominently featured conduction abnormalities, hese studies have usually not included control groups.)ne study that did include a large control group revealed that only right bundle branch block was signifiantly more common in subjects with submitral calcium.[14] The lack of a significant association of conduction bnormalities in the present study suggests that selective bias may account for a significant part of the reorted association between submitral calcium and onduction abnormalities. In contrast is the strong asociation of submitral calcium with AF.

Of potential significance is the finding of subjects ith submitral calcium and no other evidence of cardiac r systemic disease to explain their AF. This suggests hat a significant number of patients diagnosed as aving lone AF have submitral calcium as a possible rigin of the dysrhythmia. Mechanisms for AF might nclude left atrial enlargement causing temporal disersion of refractory periods in atrial tissue which would n turn predispose to reentrant rhythms such as AF. LV nflow obstruction could increase left atrial pressure and ead to left atrial enlargement.[16] Decreased LV compliance (associated with increased wall thickness) and mitral regurgitation or LV failure (which are associated with LV dilatation), or a combination of these would be expected to contribute to increased left atrial pressure and left atrial enlargement. Extension of the degenerative changes associated with submitral calcium into atrial tissue might interrupt atrial conduction and predispose to AF. Alternatively, increased stress on the mitral apparatus associated with AF might accelerate degenerative changes and lead to submitral calcium.

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Left Ventricular Volume and Ejection Fraction Response to Exercise in Aortic Regurgitation

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To test the hypothesis that left ventricular (LV) performance in aortic regurgitation (AR) can be more completely characterized by measurement of LV volumes in addition to ejection fraction (EF), 27 asymptomatic patients (Group 1), and 22 symptomatic patients (Group 2), and 10 control subjects were studied at rest and during upright bicycle exercise using the first-pass technique and a multicrystal scintillation camera. LV end-diastolic volume was measured by the area-length method.

In the control group end-diastolic volume increased 14%, end-systolic volume decreased 22%, and EF increased 22% with exercise. In contrast, in Group 1 patients with AR, end-diastolic volume was elevated at rest and during exercise. The 18% decrease in end-diastolic volume during exercise was significantly different from the control response ($p < 0.01$). End-systolic volume was also elevated at rest and during exercise, but the 30% decrease during exercise was a response not significantly different from the control. Although mean EF increased 15% in these patients, EF at peak exercise was significantly lower than that in the controls. In Group 2 patients with AR, resting EF was reduced, the EF response to exercise was abnormal, and end-diastolic and end-systolic volume responses to exericse were significantly different from those in Group 1: end-diastolic volume did not change and end-systolic volume increased. In contrast to the fairly uniform volume responses among all Group 1 patients, there were 2 subgroups based on volume changes within Group 2: 7 of 22 had a decrease in end-diastolic volume and end-systolic volume during exercise and 8 of 22 showed an increase in end-diastolic and end-systolic volume during exercise. In conclusion, LV volumes at rest and exercise give more information about LV functional reserve in symptomatic patients with AR than do EF responses alone, and may be useful in separating symptomatic patients who show a normal end-systolic volume response to exercise from those in whom worsening failure develops during exercise.

The results after valve replacement in symptomatic patients with aortic regurgitation (AR) are variable. Some patients fail to show an improvement in left ventricular (LV) function or may actually have further deterioration after valve replacement.[1] Other data suggest that resting ejection fraction (EF) improves after aortic valve replacement but that the EF response to exercise remains abnormal.[2] However, prosthetic valves are not perfect.[3] Degeneration and calcification of porcine valves have occurred more frequently in younger patients.[4,5] Because isolated AR due to rheumatic fever is most common in young men,[6] a real clinical dilemma arises concerning the optimal timing for aortic valve replacement.

Radionuclide angiography has been a useful method for noninvasive measurement of cardiac function in patients with AR. Borer et al,[7] using gated blood pool scintigraphy at rest and during supine exercise, found a variable EF response among asymptomatic patients, some patients showing an increase and others a decrease in EF during exercise. However, EF alone is both preload- and afterload-dependent. Ventricles with volume overload have abnormal loading conditions, and therefore indexes of LV function more independent of preload than EF are important in these conditions.

From the Department of Medicine, College of Physicians & Surgeons, Columbia University, New York, New York, This study was supported in part by Grants HL-21006 and HL-14148 from the U. S. Public Health Service, Bethesda, Maryland. Manuscript received June 29, 1982; revised manuscript received January 10, 1983, accepted January 17, 1983.

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It has been shown experimentally that a more complete characterization of LV performance can be achieved by measurement of LV end-diastolic and end-systolic volumes.[8] Therefore, the objective of the present study was to define, using first-pass radionuclide angiography, the response of LV volumes to upright exercise in asymptomatic and symptomatic patients with AR. The data indicate that the LV volume response to exercise delineates subgroups within the symptomatic population. In addition, this report includes the results of a validation of the radionuclide measurements of LV volumes against green dye cardiac output and contrast ventriculography performed in our laboratory.

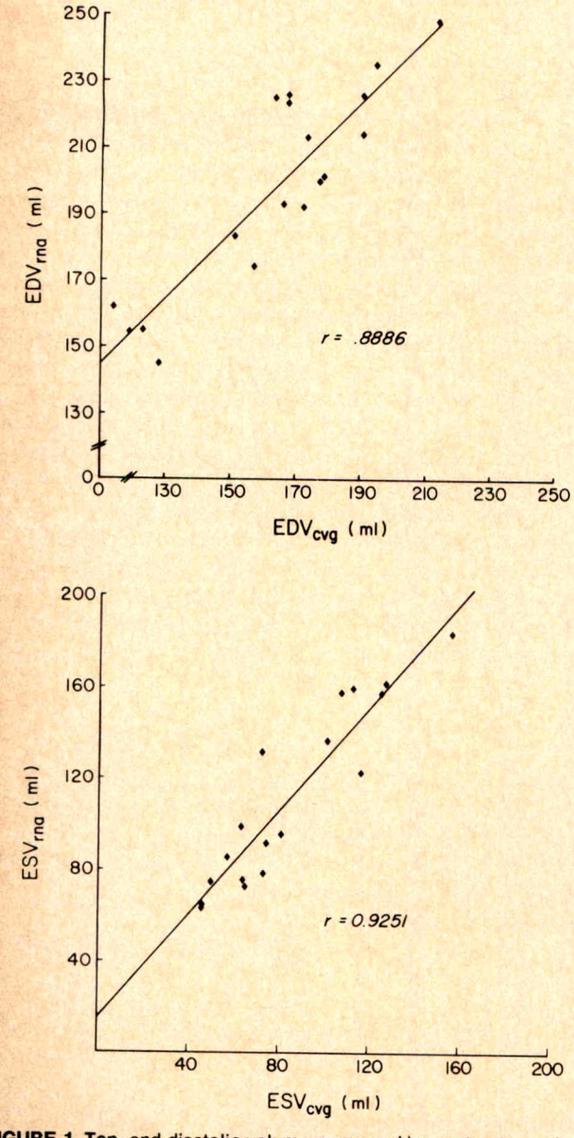

FIGURE 1. Top, end-diastolic volume measured by contrast ventriculography (EDV_{cvg}) is plotted against end-diastolic volume measured by radionuclide angiography (EDV_{rna}). **Bottom,** end-systolic volume measured by contrast ventriculography (ESV_{cvg}) is plotted against end-systolic volume measured by radionuclide angiography (ESV_{rna}).

Methods

Patient selection: All patients with AR studied in the Nuclear Cardiology Laboratory at Presbyterian Hospital from January 1979 through January 1981 were considered candidates for the study. All patients with coexisting valvular lesions, including aortic stenosis, mitral stenosis, mitral regurgitation, and coronary artery disease, were excluded. In addition, 10 healthy normal control subjects were studied.

The group consisted of 42 men and 7 women aged 17 to 78 years. All patients were referred for study because of clinical signs of AR including diastolic murmur and wide pulse pressure. Forty-one of the 49 patients had left ventricular hypertrophy on electrocardiography based on Romhilt-Estes criteria, and 40 of 49 had enlarged hearts on chest X-ray based on a cardiothoracic ratio >0.5. Twenty-seven patients were asymptomatic (Group 1) and 22 were symptomatic with either dyspnea or chest pain or both (Group 2). Twenty-six patients, including 19 of 22 patients in Group 2, had cardiac catheterization. The results of catheterization documented isolated 3+ to 4+ AR.

In the noncatheterized group, coexistent valvular lesions were ruled out by echocardiography. All patients who had cardiac catheterization had normal coronary arteries, including 25 of the 31 patients over 35 years of age. Six other patients who were over 35 and who did not have catheterization had normal EF responses to 85% age-predicted maximal heart rate and none had angina.

The 10 control subjects were all healthy male volunteers aged 22 to 46 years with a mean age of 29 ± 7 (standard deviation). None had any cardiac symptoms and all had normal cardiovascular examinations.

First-pass radionuclide angiography: Radionuclide angiography at rest and during upright bicycle exercise was performed by the first-pass technique as previously described.[9] A multiple crystal gamma camera (System Seventy-Seven, Baird Atomic) equipped with a 1-inch collimator, was used for data acquisition. Exercise was begun at the work load equivalent to stage 1 of the Bruce protocol and increased by 150 or 300 kpm/min increments and terminated by symptoms of dyspnea, leg fatigue, or achievement of 85% of age-predicted maximal heart rate. Blood pressure was measured on a cuff sphygmomanometer. Lead CS_5 of the electrocardiogram was monitored continuously and recorded at 1-minute intervals using a Hewlett-Packard recorder. At peak exercise, radionuclide angiography was repeated while the patient continued to pedal. LVEF was determined using a modification[9] of the method of Marshall et al.[10]

Left ventricular volume measurements: The LV border and the intensity and spatial distribution of background counts were defined by computer analysis..[11] An LV region of interest was determined on the basis of identification of count changes during the cardiac cycle. A representative cardiac cycle was constructed from the summation of the end-diastolic and end-systolic beats in the LV region of interest. Background was determined by a computer algorithm.[11] The LV border was defined to include all counts in the LV end-diastolic image above 21% of the highest count in the image. The use of this lower level of 21% is based on phantom studies performed with a 1.5-inch collimator.[12]

LV volumes were measured using a modification of the single plane area-length method.[13] The area of the LV silhouette was planimetered using a Hewlett-Packard desk top calculator (model 9820A). End-diastolic volumes were calculated from the equation for an ellipsoid of revolution for the single anterior projection in which end-diastolic volume (EDV) = $0.85\ A^2L$, where A = area and L = length of the major axis. Correction was made for image magnification by multi-

plying the planimetered area by the ratio of the measured width of the hard copy display of the entire collimator field of view and the measured width of a row of crystals on the detector (true area = measured area × 2.2).

A study was carried out in our laboratory to validate the area-length method for calculating end-diastolic volume from radionuclide angiograms (EDV_{rna}) against contrast ventriculography (EDV_{cvg}). In 18 patients without valvular regurgitation undergoing right and left heart catheterization, cardiac output was measured by green dye, and a first-pass radionuclide angiogram in the anteroposterior projection was performed using a multicrystal scintillation camera located in the catheterization laboratory. Immediately thereafter, a contrast left ventriculogram was performed in the shallow (15° to 20°) right anterior oblique projection.

An excellent correlation was found between EDV_{cvg} and EDV_{rna} with an r value of 0.89 and a standard error of the estimate (SEE) of 14.5 ml (Fig. 1, top). The radionuclide volumes consistently overestimated the contrast ventriculographic volumes. A regression equation was derived for the radionuclide data: $y = 0.84x - 10.3$ in which y = corrected end-diastolic volume and x = measured radionuclide volume. Stroke volume was calculated as end-diastolic volume times EF, and end-systolic volume as end-diastolic volume minus stroke volume. When the ESV_{rna} was plotted versus ESV_{cvg} there was an excellent correlation, with an r value of 0.93 and an SEE of 15.5 ml (Fig. 1, bottom).

To test the reproducibility of calculated LV volumes in patients with cardiac dilatation, 8 patients with cardiac dilatation had serial rest and exercise studies. The standard deviation of replicate measurements was ±7.1 ml for ΔEDV and ±8.0 ml for ΔESV, resulting in 95% confidence limits, close to the value of 15 ml reported by Scholz et al.[11] Therefore, a significant change for any individual value of LV volumes was defined as a change >15 ml.

Of the 21 patients with AR who were catheterized, 10 met the following criteria: (1) radionuclide studies performed within 3 months of catheterization, and (2) contrast ventriculograms of good enough quality for volume measurements. In these 10 patients, when end-diastolic volumes measured by radionuclide angiocardiography was compared with end-diastolic volumes measured by contrast ventriculography, there was a good correlation, with an r value of 0.93.

Statistical analysis: Tests of hypotheses relating to group means were performed by analysis of variance or by the nonparametric Kruskal-Wallis procedure when the variables were not normally distributed within groups, as was the case for LV volumes.[14] Correlations between LV volume and EF were determined using the Wilcoxon procedure. Differences were termed significant if the test statistic exceeded the critical value for the 5% level.

Results

Control subjects: The results of the study are presented in Tables I to III and Figures 2 to 5. In the control subjects the exercise duration was 12 ± 2 minutes and total work load achieved was 86 ± 25 kJ. Heart rate increased during exercise from 80 ± 11 to 162 ± 14 beats/min. Systolic blood pressure increased during exercise from 124 ± 10 to 174 ± 27 mm Hg, whereas diastolic blood pressure did not change significantly (80 ± 7 mm Hg at rest and 78 ± 7 mm Hg during exercise). End-diastolic volume at rest was 64 ± 16 ml/m² and increased during exercise to 73 ± 17 ml/m² ($p < 0.05$) (Fig. 2). End-systolic volume was 27 ± 10 ml/m² at rest

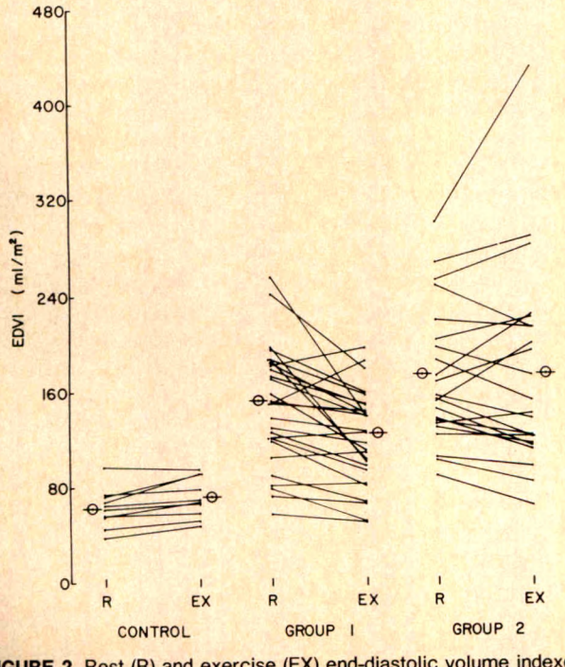

FIGURE 2. Rest (R) and exercise (EX) end-diastolic volume indexes (EDVI) for controls and for 2 AR patient groups are shown. EDVI increased significantly in controls ($p < 0.05$), decreased significantly in AR Group 1 ($p < 0.01$), and did not change significantly in AR Group 2. Mean values are indicated by **circles.**

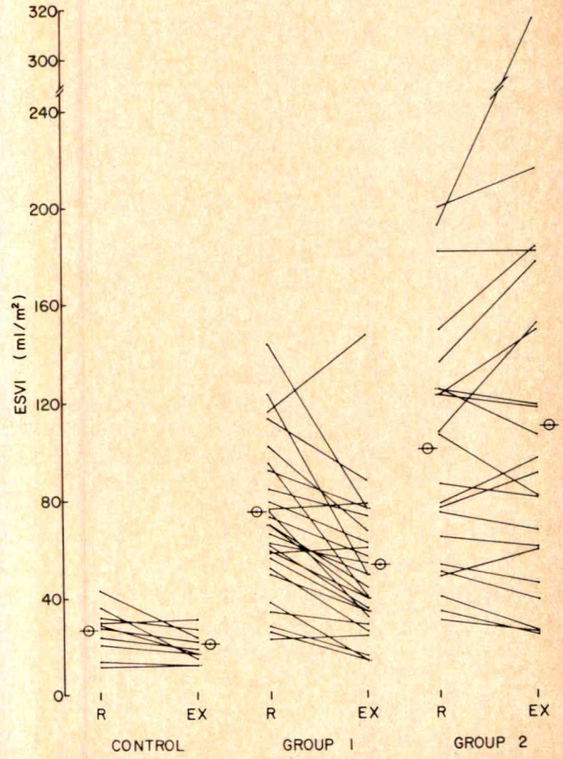

FIGURE 3. Rest (R) and exercise (EX) end-systolic volume indexes (ESVI) for controls and 2 AR patient groups are shown. ESVI decreased significantly in controls ($p < 0.05$), decreased significantly in AR Group 1 ($p < 0.01$), and did not change significantly in AR Group 2.

TABLE I Asymptomatic AR Patients (Group 1)

	LVEF (%)			LVEDVI (ml/m²)			LVESVI (ml/m²)			SVI (ml/m²)		
Pt	R	EX	ΔEF	R	EX	ΔEDVI	R	EX	ΔESVI	R	EX	ΔSVI
1	53	60	+7	126	98	−28	59	39	−20	67	59	−8
2	52	60	+8	198	101	−95	95	40	−55	103	61	−37
3	52	65	+13	257	140	−115	123	49	−74	134	91	−43
4	49	65	+16	138	127	−10	70	44	−26	68	83	+15
5	53	69	+16	105	110	+5	49	34	−15	56	76	+20
6	56	73	+17	58	51	−7	26	14	−12	32	37	+5
7	47	57	+10	150	144	−6	79	62	−17	71	82	+11
8	53	58	+5	119	81	−38	56	34	−22	63	47	−16
9	49	58	+9	150	186	+36	76	78	+2	74	108	+34
10	60	69	+9	187	103	−84	75	32	−43	112	71	−41
11	52	59	+7	152	140	−12	73	57	−16	79	83	+4
12	56	66	+10	159	111	−48	70	38	−32	89	73	−16
13	41	58	+17	243	180	−63	143	76	−67	100	104	+4
14	58	80	+22	90	69	−21	38	14	−24	52	55	+3
15	43	55	+12	179	148	−31	102	67	−35	77	81	+4
16	53	70	+17	130	117	−13	61	35	−26	69	82	+13
17	57	72	+15	121	94	−27	52	26	−26	69	68	−1
18	46	61	+15	122	125	+3	66	49	−17	56	76	+20
19	64	64	0	173	151	−22	62	54	−8	111	97	−14
20	55	49	−6	186	143	−43	84	73	−9	102	70	−32
21	69	62	−7	188	158	−30	58	60	+2	130	98	−32
22	53	52	−1	196	159	−40	92	76	−16	104	83	−21
23	54	56	+2	73	67	−6	34	29	−5	39	38	−1
24	63	68	+5	77	51	−26	28	16	−12	49	35	−13
25	71	71	0	80	82	+2	23	24	+1	57	58	+1
26	34	37	+3	171	140	−31	113	88	−25	58	52	−6
27	36	26	−10	182	197	+15	116	146	+30	66	51	−15
Mean ± 1 SD	53 ± 9	61 ± 11	+8 ± 8	149 ± 50	121 ± 40	−27 ± 33	71 ± 31	50 ± 28	−21 ± 21	77 ± 26	71 ± 20	−6 ± 20

ΔEDVI = change in end-diastolic volume index; ΔEF = change in ejection fraction; ΔESVI = change in end-systolic volume index; EX = exercise; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; Pt = patient; R = rest; SD = standard deviation; SVI = stroke volume index; ΔSVI = change in stroke volume index.

and decreased to 21 ± 6 ml/m² during exercise ($p < 0.05$) (Fig. 3). Therefore, stroke volume increased from 37 ± 8 ml/m² to 52 ± 12 ml/m² ($p < 0.05$) and EF increased from 59 ± 6% to 72 ± 5% ($p < 0.05$) (Fig. 4).

Clinical characteristics of patients with AR: The patients in Group 2 were significantly older than those in Group 1 (47 ± 17 versus 38 ± 15 years, $p < 0.01$). A similar number of patients in Group 2 had LV hypertrophy on electrocardiogram (20 of 22, 91%) as in Group 1 (22 of 27, 81%). A similar number of patients in Group 2 had enlarged hearts on chest X-ray (17 of 22, 77%) as in Group 1 (18 of 27, 67%).

AR Group 1: Exercise duration in AR Group 1 was 10 ± 2 minutes, significantly less than that in the controls ($p < 0.01$); the work load achieved, 52 ± 22 kJ, was also significantly less than that in the controls ($p < 0.01$) (Table I). Diastolic time per minute decreased from 35 ± 4 s/min to 30 ± 5 s/min ($p < 0.01$).

In AR Group 1, the resting heart rate of 80 ± 16 beats/min was not significantly different from that of the control subjects. During exercise, heart rate increased to 149 ± 25 beats/min, a value also not significantly different from that of the controls. At rest, the systolic blood pressure (139 ± 17 mm Hg) was significantly higher and the diastolic blood pressure (63 ± 19 mm Hg) lower in AR Group 1 than in the controls ($p < 0.05$). However, during exercise the systolic and diastolic blood pressure (195 ± 25 mm Hg, 81 ± 15 mm Hg) was not significantly different from that of the control subjects.

In AR Group 1, the end-diastolic volume at rest was significantly greater than that of the controls ($p < 0.01$) (Table I, Fig. 2) and decreased during exercise to a value that was significantly higher than the exercise end-diastolic volume observed in the control subjects. The decrease in end-diastolic volume during exercise in AR Group 1 was a significantly different response from the increase during exercise observed in the control subjects ($p < 0.01$) (Fig. 5). The end-systolic volume at rest in Group 1 was significantly larger than that in the control subjects ($p < 0.01$) (Fig. 3). During exercise, end-systolic volume decreased in AR Group 1, but the value for exercise end-systolic volume was significantly larger than the end-systolic volume at peak exercise observed in the control subjects ($p < 0.01$). The change in end-systolic volume during exercise was not significantly different between the 2 groups (Fig. 5).

The EF at rest in AR Group 1 was not significantly different from that of the control subjects, and it increased during exercise ($p < 0.05$) (Fig. 4). Although the exercise EF in AR Group 1 was significantly lower than that of the control subjects, the change in EF observed during exercise was not significantly different between the 2 groups.

Twenty of the 27 patients in AR Group 1 showed a significant decrease in end-diastolic volume from rest to exercise (Table I). Twenty-two of 27 showed a significant decrease in end-systolic volume. Only 2 patients had a significant increase in end-diastolic volume during exercise (Patients 9 and 27). Only 1 patient had a sig-

TABLE II Symptomatic AR Patients (Group 2)

	LVEF (%)			LVEDVI (ml/m²)			LVESVI (ml/m²)			SVI (ml/m²)		
Pt	R	EX	ΔEF	R	EX	ΔEDVI	R	EX	ΔESVI	R	EX	ΔSVI
1	53	60	+7	106	98	−8	50	39	−11	56	59	+3
2	57	63	+6	123	122	−1	53	45	−8	70	77	+7
3	64	69	+5	112	85	−27	40	26	−14	72	59	−13
4	45	46	+1	135	124	−11	74	67	−7	61	57	−4
5	54	51	−3	169	195	+26	78	96	+18	91	99	+8
6	47	38	−9	254	283	+29	135	175	+40	119	108	−11
7	63	50	−13	130	117	−13	48	58	+10	82	59	−23
8	51	45	−6	248	213	−35	122	117	−5	126	96	−30
9	53	46	−7	137	112	−25	64	60	−4	73	52	−21
10	79	78	−1	145	114	−31	30	25	−5	115	89	−26
11	62	64	+2	90	66	−24	34	24	−10	56	42	−14
12	45	42	−3	157	138	−19	86	80	−6	71	58	−13
13	31	34	+3	154	122	−32	106	81	−25	48	41	+7
14	37	32	−5	197	174	−23	124	118	−6	73	56	−17
15	27	18	−9	203	221	+18	148	181	+33	55	40	−15
16	37	27	−10	301	430	+129	190	314	+124	111	116	+5
17	18	16	−2	220	214	−6	180	180	0	40	34	−6
18	33	31	−2	187	153	−34	125	106	−19	62	47	−15
19	30	25	−5	153	200	+47	107	150	+43	46	50	+4
20	43	36	−7	133	141	+8	76	90	+14	57	51	−6
21	30	28	−2	175	205	+30	122	148	+26	53	57	+4
22	26	23	−3	268	278	+10	198	214	+16	70	64	−6
Mean ±1 SD	45 ± 15	42 ± 17	−3 ± 5	173 ± 57	173 ± 83	+0.5 ± 37	100 ± 51	109 ± 73	+9 ± 32	73 ± 25	64 ± 23	−9 ± 11

ΔEDVI = change in end-diastolic volume index; ΔEF = change in ejection fraction; ΔESVI = change in end-systolic volume index; EX = exercise; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; Pt = patient; R = rest; SD = standard deviation; SVI = stroke volume index; ΔSVI = change in stroke volume index.

TABLE III LV Volume Responses in Symptomatic AR Patients

	ΔESV		
ΔEDV	Decrease	No Change	Increase
Decrease	7	4	0
No change	0	2	0
Increase	1	0	8

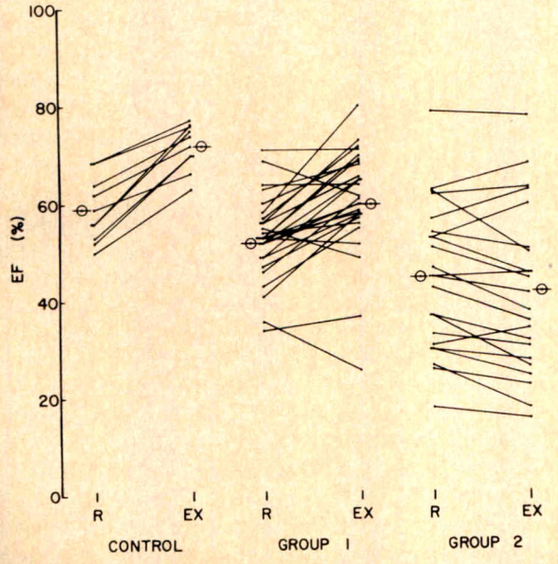

FIGURE 4. Rest (R) and exercise (EX) ejection fraction for controls and 2 AR patient groups are shown. EF increased significantly in AR Group 1 ($p < 0.01$) and showed a small but significant decrease in AR Group 2 ($p < 0.05$).

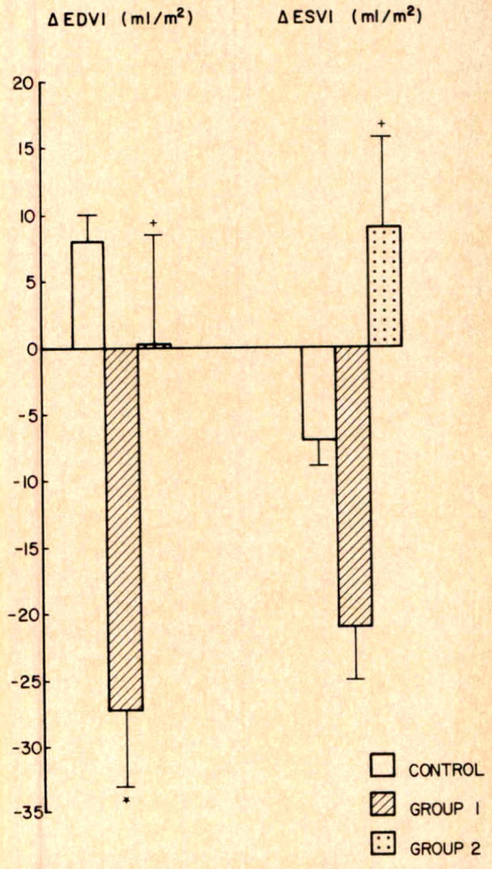

FIGURE 5. The changes in LV volume are depicted for controls and the 2 AR patient groups. The **error bars** represent 1 standard of the mean, the **asterisk** denotes a value significantly different from that in the controls, and the **plus signs** denote a value significantly different from that in Group 1. Abbreviations as in Figures 2 and 3.

nificant increase in end-systolic volume (Patient 27). This patient had a concomitant decrease in EF and an increase in end-diastolic volume.

AR Group 2: Exercise duration in AR Group 2 was 7 ± 2 minutes, significantly lower than that of the controls ($p < 0.01$) and lower than that of AR Group 1 patients ($p < 0.05$). Total work load achieved was 31 ± 16 kJ, significantly lower than that of the controls ($p < 0.01$) and lower than that of AR Group 1 patients ($p < 0.01$). Diastolic time per minute during exercise in AR Group 2 decreased from 34 ± 4 s/min to 31 ± 4 s/min ($p < 0.01$). The decrease in diastolic time per minute during exercise was not significantly different from that of AR Group 1 patients (−3 ± 3 versus −5 ± 6 s/min).

In AR Group 2 the heart rate at rest (82 ± 14 beats/min) was not significantly different from that of the control subjects or of AR Group 1 patients. During exercise the heart rate increased to 136 ± 27 beats/min, a value less than that of the controls ($p < 0.01$) but not significantly different from that of AR Group 1 patients. At rest systolic blood pressure in AR Group 2 (143 ± 25 mm Hg) was significantly higher and the diastolic blood pressure (63 ± 22 mm Hg) lower than the control subjects; pressures increased during exercise to 190 ± 34 and 69 ± 24 mm Hg, respectively. During peak exercise the systolic and diastolic blood pressures were not significantly different among the 3 groups.

In AR Group 2, the end-diastolic volume at rest was significantly greater than that of the controls ($p < 0.01$), but not significantly different than that of Group 1 patients (Fig. 2). End-diastolic volume did not change during exercise in this group, a response that was significantly different from the change during exercise in AR Group 1 ($p < 0.01$) (Fig. 5). The end-systolic volume at rest in AR Group 2 patients was significantly larger than that of the controls ($p < 0.01$) but not significantly different from that in AR Group 1 (Fig. 3). End-systolic volume increased during exercise in AR Group 2 patients to a value significantly larger than that of the controls ($p < 0.01$), and also significantly larger than that in AR Group 1 ($p < 0.01$). In addition, the change in end-systolic volume during exercise in AR Group 2 was significantly different from the change during exercise in AR Group 1 ($p < 0.01$) (Fig. 5).

In AR Group 2 the resting EF was significantly lower than that in AR Group 1 and that in the control subjects. During exercise the EF decreased slightly, but significantly ($p < 0.05$) (Fig. 4). The ejection fraction at peak exercise was significantly lower in AR Group 2 than in AR Group 1 or in control subjects.

Within AR Group 2, there were several subgroups based on combined LV volume EF responses (Tables II and III). Seven patients (Patients 1, 3, 4, 10, 11, 13, and 18) had a significant decrease in end-diastolic volume and end-systolic volume. Of this group, 2 (Patients 1 and 3) had a borderline normal EF fraction response to exercise. Eight patients (Patients 5, 6, 15, 16, and 19–22) had a significant increase in end-diastolic and end-systolic volume. Of this group, 7 (Patients 6, 15, 16, and 19–22) had reduced resting ejection fractions and a further decrease in ejection fraction during exercise. Of the remaining 7 patients in AR Group 2, the volume response was variable. Four (Patients 8, 9, 12, and 14) had a significant decrease in end-diastolic volume with a smaller nonsignificant decrease in end-systolic volume; 2 (Patients 2 and 17) had no significant change in either end-diastolic or end-systolic volume, and 1 (Patient 7) had a decrease in end-diastolic volume and an increase in end-systolic volume (Table III).

Discussion

The mean values for end-diastolic volume at rest and during exercise obtained in the control subjects were not different from those reported by Rerych et al[13] in normal volunteers using a similar upright bicycle exercise protocol and the first-pass radionuclide technique.[13] In addition, the directional changes in all parameters were similar to those reported by Poliner et al[15] who compared the effects of supine and upright exercise on LV volumes and EF in normal subjects.

The results in asymptomatic patients with AR differ from those reported by Dehmer et al.[16] In their study, end-diastolic and end-systolic volumes at rest in asymptomatic patients with AR were significantly lower than the values in our asymptomatic AR group. During supine exercise there was no change in mean end-diastolic or end-systolic volumes or EF in the asymptomatic patients with AR studied by Dehmer et al,[16] whereas EF increased and end-diastolic and end-systolic volume decreased in our Group 1. One possible explanation for these different results are differences in protocol (supine versus upright exercise). Recently, Marx et al[17] showed that patient position significantly influences the exercise EF response in AR, probably because of differences in LV loading between the supine and upright positions. Another possible explanation is differences in patient selection. Sixty-seven percent of patients in our asymptomatic AR group had cardiac enlargement on chest X-ray and 81% had LV hypertrophy on the electrocardiogram. These findings correlated with the elevated sting end-diastolic volumes. The value for resting end-systolic volume in our asymptomatic AR Group 1 patients of 71 ± 31 ml/m^2 was not significantly different from the value of 62 ± 14 ml/m^2 that was observed for 10 asymptomatic patients with AR studied by contrast ventriculography and reported on by Osbakken et al.[18]

Regurgitant volume is an important contributor to end-diastolic volume in patients with AR. During exercise, diastolic time per minute decreased 5 seconds in AR Group 1 patients. The reduction in regurgitant volume is the most likely explanation for the large decrease in end-diastolic volume which occurred during exercise. This interpretation is consistent with other studies of patients with AR during pacing in which LV end-diastolic pressure decreased as diastolic time per minute was reduced by the faster heart rate.[19]

End-systolic volume was increased at rest in asymptomatic Group 1 patients with AR. Other investigators have observed that cardiac enlargement in volume overloaded hearts is accompanied by elevations in both end-diastolic and end-systolic volumes with maintenance of a normal relation between stroke volume and end-diastolic volume.[20]

The fact that mean end-systolic volume was increased not only at rest but also at peak exercise in Group 1 patients and that the exercise EF was below that of the controls may indicate impairment of myocardial contractility in Group 1 patients. In the study of Dehmer et al,[16] mean end-systolic volume at peak exercise was also higher than that in the controls. In the ventriculographic study of Osbakken et al,[18] plots of resting end-systolic stress and end-systolic volume index were made for control subjects and for asymptomatic and symptomatic patients with AR. These investigators found that the data for the 3 groups fell on 3 separate curves, with the curve for the asymptomatic patients with AR intermediate between the other 2 groups.

The decrease in end-systolic volume during exercise in the asymptomatic AR group was greater than that in the controls; however, when expressed as a percentage of resting end-systolic volume, there was no difference from the control group. The decrease in end-systolic volume seen in upright exercise in normal subjects is a result of the combination of the effects of increased myocardial contractility and decreased afterload.[21] Therefore, the decrease in end-systolic volume with exercise in Group 1 patients suggests either that afterload during exercise is lower in this group than in Group 2 patients who show an increase in end-systolic volume during exercise, or that the ventricles of Group 1 patients are able to respond to increased circulating catecholamines during exercise, or both.

In contrast to the fairly homogeneous volume response in Group 1, inspection of the data (Fig. 2, 3, and 5) indicate that the responses to exercise in Group 2 were not uniform. Two distinct subgroups can be identified. In 1 subgroup (7 patients) end-diastolic volume decreased as diastolic time per minute and probable net regurgitation decreased. In this same subgroup end-systolic volume simultaneously decreased. In the second subgroup of 8 patients in AR Group 2, concomitant increases in both end-diastolic and end-systolic volumes and a decrease in EF during exercise indicate the effect of exercise in inducing a worsening of preexisting LV failure.

In summary, there are distinctly different patterns of LV volume change during exercise among patients with AR. There is a younger, asymptomatic subgroup in whom the end-diastolic volume decreases during exercise as diastolic time per minute decreases with rapid heart rate, suggesting that regurgitant volume is a major determinant of resting end-diastolic volume in this group. In this same group end-systolic volume decreases while EF increases, suggesting a positive inotropic response to exercise. In contrast, among older, symptomatic patients with AR, there is a subgroup with a pattern of volume change similar to that in Group 1, and another subgroup in whom LV failure clearly develops during exercise. Further study is needed to determine whether LV volume response during exercise in patients with AR is a useful parameter that can be combined with other parameters to help predict the optimal time for aortic valve replacement.

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Atrial Systole and Left Ventricular Filling in Hypertrophic Cardiomyopathy: Effect of Verapamil

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Many patients with hypertrophic cardiomyopathy (HC) have impaired left ventricular (LV) rapid diastolic filling. To quantitate the contribution of atrial systole to LV filling, we used radionuclide angiography to study 30 normal volunteers and 42 patients with HC before and after oral administration of verapamil (320 to 560 mg/day). LV time-activity curves were constructed by combined forward and reverse gating from the R wave, and the onset of atrial systole was determined by the P-R interval. The percent of LV stroke volume filled during rapid diastolic filling and atrial systole was then computed. Peak LV filling rate during rapid diastolic filling was expressed in end-diastolic volume (EDV)/second. Peak rate of rapid diastolic filling was not different in normal patients and those with HC (3.3 ± 0.6 versus 3.3 ± 1.1 EDV/s) and was within the normal range in 34 patients with HC (81%). However, the contribution to LV filling volume by rapid diastolic filling was diminished in patients with HC (83 ± 7% normal, 67 ± 17% HC, $p < 0.001$) and the contribution of atrial systole was increased (16 ± 8% normal, 31 ± 18% HC, $p < 0.001$). LV filling volume during atrial systole was above the upper normal limit of 31% in 17 patients (40%), including 13 patients with a normal peak filling rate. After verapamil, peak filling rate increased (to 4.2 ± 1.2 EDV/s, $p < 0.001$), percent LV filling during rapid diastolic filling increased (to 83 ± 7%, $p < 0.001$), and percent LV filling during atrial systole decreased (to 16 ± 9%, $p < 0.001$). Percent LV filling volume during atrial systole was abnormal after verapamil in only 3 patients (7%). Hence, although the peak rate of rapid diastolic filling may be normal in patients with HC, the contribution to LV filling by rapid diastolic filling is reduced and that of atrial systole is thereby increased. Increased rate and magnitude of rapid diastolic filling during verapamil is associated with decrease and normalization of the contribution of atrial systole to LV filling. These data suggest that many patients with HC are at risk of hemodynamic decompensation with the onset of atrial fibrillation or other tachyarrhythmias and loss of the atrial contribution to LV filling. This risk may be reduced during verapamil therapy.

Many patients with hypertrophic cardiomyopathy (HC) have abnormal left ventricular (LV) filling during early diastole, manifested by impaired isovolumic relaxation, reduced rapid diastolic filling periods, and diminished rate of rapid diastolic filling.[1–7] These factors may reduce the contribution of rapid diastolic filling to total LV filling volume, and the contributions of slow diastolic filling or atrial systole to LV filling might then be increased. Because atrial fibrillation, atrial flutter, and ventricular tachycardia are common complications of HC,[8–10] an increased dependence on atrial systole for LV filling may place many patients at risk of hemodynamic decompensation with the onset of these arrhythmias and the loss of synchronized atrial contraction.

In the current study, we used LV time-activity curves obtained by radionuclide angiography to quantitate the contributions of rapid diastolic filling and atrial systole to LV filling in patients with HC. We have also studied the effects of oral verapamil therapy to determine if improved isovolumic relaxation[11] and an increased rate of rapid diastolic filling[7] observed during verapamil administration are associated with a reduction in the contribution of atrial systole to LV filling.

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Methods

Patient selection: We studied 57 patients, aged 21 to 69 years (mean 44), with HC. All patients were in normal sinus rhythm. In each patient, the diagnosis of HC was based on echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of other acquired or congenital heart disease.[12] Disproportionate septal thickening with respect to the LV free wall (septal-to-free wall ratio ≥1.3) was identified in 53 patients. In the other 4 patients, 2-dimensional echocardiography demonstrated regional disproportionate hypertrophy in the posterior septum or anterolateral LV free wall.[13] Cardiac catheterization in 55 patients demonstrated LV outflow tract obstruction at rest (gradient ≥30 mm Hg) in 21 patients (38%). In 25 patients (45%) without resting obstruction, ≥30 mm Hg subvalvular gradient developed during provocation with amyl nitrate inhalation, intravenous isoproterenol infusion, or the Valsalva maneuver. In 9 patients (16%), no gradient was elicited either at rest or with provocation. In both patients not catheterized, systolic anterior motion of the anterior mitral valve was demonstrated at rest by echocardiography.

We also studied 30 normal volunteers, aged 21 to 63 years, to determine the normal values for the radionuclide measurements. These subjects had no evidence of cardiovascular or pulmonary disease. Cardiac catheterization was not performed, but physical examination (including blood pressure), chest X-ray, electrocardiography, and M-mode echocardiography gave normal results in all subjects.

Drug administration: In patients with HC, control radionuclide studies were performed ≥48 hours after the cessation of propranolol and all other cardiac medications except diuretics. After the control study, oral verapamil was administered. Therapy was initiated at a dose of 240 mg daily in divided doses and was gradually increased every 36 to 48 hours to a dose of 480 to 640 mg daily. The final verapamil dosage was determined by the clinical response of each patient and was limited in some patients because of atrioventricular dissociation, Mobitz I second-degree atrioventricular block, or systemic hypotension. The final daily verapamil dose was 320 mg in 10 patients (17%), 360 mg in 15 patients (26%), 400 mg in 1 patient (2%), 480 mg in 15 patients (26%), 560 mg in 1 patient (2%), and 640 mg in 1 patient. Radionuclide angiography was repeated after each patient received what was considered the optimal verapamil dosage for at least 36 hours.

Gated equilibrium blood pool scintigraphy: Radionuclide cineangiography was performed at rest using red blood cells labelled in vivo with 15 to 20 mCi of technetium-99m.[14] Blood pressure was measured by sphygmomanometry in the supine position at the time of each radionuclide study. Imaging was performed in the supine position with a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle from other cardiac structures. The cardiac image sequence spanning the average cardiac cycle was constructed from several hundred cardiac cycles by computer-based electrocardiographic gating, using list-mode data acquisition (framing rate up to 100 images/s).[7,15] High-temporal resolution LV time-activity curves were generated from the cardiac image sequence after background correction. Extrasystolic and postextrasystolic cardiac cycles were excluded, and the diastolic portion of the time-activity curve was constructed by combined forward-gating and reverse-gating from the R wave.[16,17] The time-activity curve represents a measure of relative LV volume changes with time throughout the cardiac cycle.

LV ejection fraction was automatically determined by computer analysis of the time-activity curve.[15] Peak rate of LV filling during the rapid filling phase of diastole was computed by fitting a third-order polynomial function to the rapid filling portion of the time-activity curve, using a least-squares technique.[7,18] Peak filling rate was computed in counts per second, normalized for the number of counts at end-diastole, and expressed as end-diastolic volume per second (EDV/s). The time to peak filling rate was measured from end-systole (minimal volume on the time-activity curve) to the time of peak left ventricular filling rate.

Two other indexes of LV diastolic filling were also computed: relative LV filling volume during rapid diastolic filling and relative filling volume during atrial systole. These measurements were obtained in all 30 normal volunteers. However, these measurements could be performed in only 42 patients with HC in whom the rapid diastolic filling and atrial systolic portions of the time-activity curve were clearly separated by a diastasis interval (or slow filling phase) (Fig. 1).

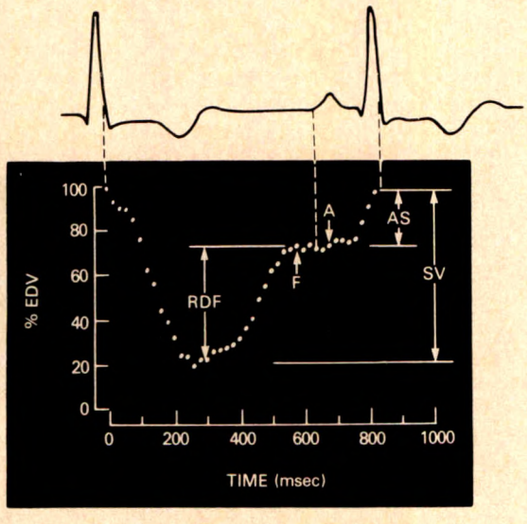

FIGURE 1. Left ventricular time-activity curve obtained at rest in a patient with hypertrophic cardiomyopathy. Heart rate is 70 beats/min. Each point represents 20 ms. Termination of rapid diastolic filling (**arrow F**) is determined visually by 2 observers. Onset of atrial systole (**arrow A**) is determined automatically by subtracting the P-R interval (140 ms) and the interval from the onset of QRS to point of R-wave gating (60 ms) from the cardiac cycle length and then adding 40 ms for assumed atrial electrical-mechanical delay. Left ventricular filling volume during rapid diastolic filling (RDF) and atrial systole (AS) are expressed relative to total stroke volume (SV). EDV = end-diastolic volume.

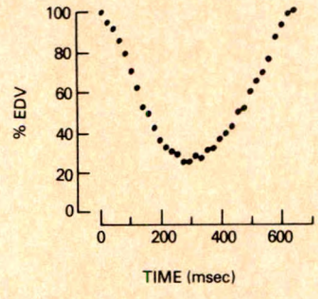

FIGURE 2. Time-activity curve obtained at rest from a patient with hypertrophic cardiomyopathy. The heart rate is 96 beats/min. Unlike the time-activity curve in Figure 1, no diastasis interval is evident, and termination of rapid diastolic filling cannot be differentiated from onset of atrial systole. EDV = end-diastolic volume.

In the other 15 patients, no diastasis interval was evident under control conditions, and rapid diastolic filling and atrial systole could not be distinguished (Fig. 2). Patients without a discernible diastasis interval had a faster heart rate than did patients with a diastasis interval (92 ± 14 [SD] versus 71 ± 12 beats/min; $p < 0.001$), but did not differ with respect to age, sex, or indexes of LV function such as ejection fraction or peak filling rate. Eleven of 15 patients without a discernible diastasis interval (73%) had a heart rate ≥90 beats/min, which compares with only 3 of 42 patients with a diastasis interval (7%). The 15 patients in whom rapid diastolic filling could not be distinguished from atrial systole under control conditions were excluded from further analysis. Thus, data regarding relative LV filling volumes during rapid filling and during atrial systole before and after verapamil were computed in 42 patients. There were 26 men and 16 women.

Left ventricular filling during rapid diastolic filling: The termination of the rapid filling phase of the time activity curve was determined by visual inspection (Fig. 1), and the relative LV filling volume occurring during rapid diastolic filling was computed as a percentage of total LV stroke volume. To minimize the effect of random noise in the curve, the volume represented by the point on the curve selected as termination of rapid filling was averaged with the volume represented by the points on either side of the point in question to yield a 3-point average. Because this visual selection process is subjective, each curve was analyzed by 2 independent observers, both of whom were unaware of whether the curve represented a normal study, a control study, or a verapamil study. Percent of LV filling volume during rapid filling for each curve was chosen as the average of the 2 observers' calculations. A close agreement was reached between the 2 observers for normal volunteers ($r = 0.97$, standard error [SE] = 1.75) and for patients with HC ($r = 0.89$, SE = 6.90).

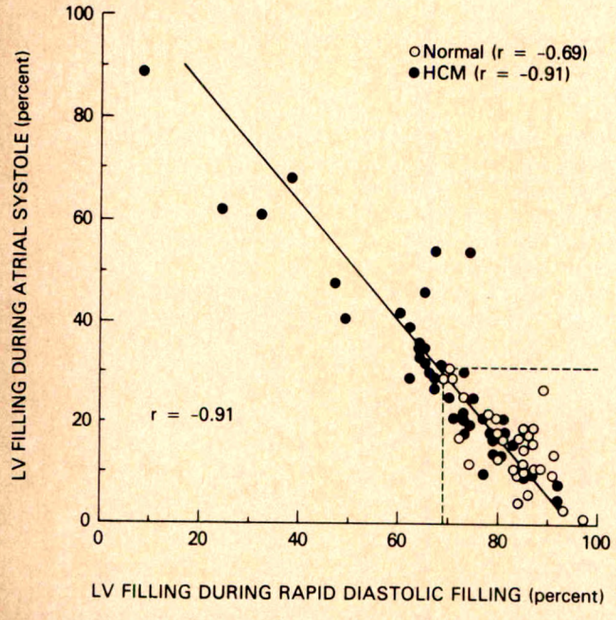

FIGURE 3. Left ventricular (LV) filling volume during atrial systole plotted as a function of LV filling volume during rapid diastolic filling in normal volunteers (**open circles**) and patients with hypertrophic cardiomyopathy (HCM) (**closed circles**). Both filling volumes are expressed as percentages of total LV stroke volume. **Dashed lines** indicate lower limit of normal for filling during rapid diastolic filling (69%) and upper limit of normal for filling during atrial systole (31%). The **solid line** indicates the linear regression line.

Left ventricular filling during atrial systole: To determine the onset of atrial systole, the total duration of the P-R interval (onset of P wave to onset of QRS) plus the interval from the onset of QRS to instant of R-wave gating (peak negative R-to-S transition) was measured to the nearest 20 ms from an electrocardiographic rhythm strip obtained during the radionuclide data acquisition. This sum was subtracted from the cardiac cycle length to indicate the point on the time activity curve representing the onset of atrial electrical activation; 40 ms was added to this value to account for atrial electrical-mechanical delay, and this new point on the curve was chosen as the onset of mechanical atrial systole (Fig. 1). Relative LV filling during atrial systole was then computed as a percentage of the total LV stroke volume. As in the determination of rapid diastolic filling volume, a 3-point average was performed about the point on the curve selected as the onset of atrial systole to minimize the influence of random noise. The P-R interval and the interval from the onset of QRS to the instant of R-wave gating were measured manually without knowledge of whether a study was performed during control conditions or during verapamil administration. The remaining computations were performed automatically by computer processing. A good correlation ($r = 0.91$, SE = 6.90) was observed between the percentage of LV filling during rapid diastolic filling measured visually (average of 2 observers) and the percentage of LV filling during atrial systole measured automatically (Fig. 3).

Reproducibility of radionuclide measurements: The reproducibility of LV ejection fraction, peak filling rate, and time to peak filling rate by radionuclide angiography have been reported previously in patients with HC.[7] To determine the reproducibility of the percentage of LV filling during rapid diastolic filling and during atrial systole, we studied 25 other patients with HC in whom the diagnosis was established by M-mode echocardiographic criteria. Each patient had a septal-to-free wall ratio >1.3. Two radionuclide studies were performed after a single injection of technetium-99m ≥48 hours after the cessation of all cardiac medications.

Statistical methods: Data were analyzed by the *t* test, using unpaired and paired data as appropriate, and by linear regression analysis. Normal limits for the percentage of LV filling during rapid diastolic filling and during atrial systole were defined by the 95% confidence limits obtained in normal volunteers (mean ± 2 standard deviations).

Results

Normal data: LV ejection fraction, peak LV filling rate, and time to peak filling rate in normal volunteers (Table I) were within the previously defined normal range for our laboratory.[7] Peak filling rate ranged from 2.5 to 5.0 EDV/s and time to peak filling rate from 88 to 180 ms. LV filling volume during rapid diastolic filling ranged from 69 to 97% of the LV stroke volume (mean 83 ± 7% [SD]), and filling volume during atrial systole ranged from 0 to 31% of stroke volume (mean 16 ± 8%). The 2 mean values do not total 100% because of the small contribution of slow diastolic filling to LV filling volume. On the basis of the distribution of these normal data, the lower limit of normal (95% confidence limit) for filling volume during rapid diastolic filling was 69%, and the upper limit of normal for filling volume during atrial systole was 31% (Fig. 3). The peak rate of filling during rapid diastolic filling did not correlate with the filling volume during either rapid diastolic filling ($r = 0.35$) or atrial systole ($r = 0.51$).

TABLE I Radionuclide Variables Describing Left Ventricular Diastolic Filling

	Normal Volunteers (n = 30)	Hypertrophic Cardiomyopathy (n = 42)		
		Control	Verapamil	p
Heart rate (beats/min)	68 ± 8	71 ± 12	67 ± 9	<0.01
LV ejection fraction (%)	55 ± 6	75 ± 10*	74 ± 10*	NS
LV diastolic filling				
Peak LV filling rate (EDV/s)	3.3 ± 0.6	3.3 ± 1.1	4.2 ± 1.2*	<0.001
Time to peak LV filling rate (ms)	139 ± 25	177 ± 38*	164 ± 24*	<0.01
LV filling volume during RDF (%)	83 ± 7	67 ± 17*	83 ± 7	<0.001
LV filling volume during AS (%)	16 ± 8	31 ± 18*	16 ± 9	<0.001

Data are means ± standard deviation.
AS = atrial systole; EDV = end-diastolic volume; LV = left ventricular; NS = not significant; RDF = rapid diastolic filling.
Statistical significance compared with normal volunteers: * p <0.001.

The contribution of atrial systole to LV filling in normal volunteers is in close agreement with the contrast angiographic data of Hammermeister and Warbasse[19] and the echocardiographic data of Decoodt et al,[20] in which the mean normal contribution of atrial systole to the LV stroke volume was 16%.

Hypertrophic cardiomyopathy: *Control data:* LV ejection fraction in the 42 patients with HC ranged from 50 to 98% (mean 75 ± 10%) and was above the upper limit of normal (72%) in 29 patients. Peak LV filling rate ranged from 1.0 to 6.2 EDV/s and was within the normal range (≥2.5 EDV/s) in 34 patients. Hence, peak filling rate was not different in normal patients and those with HC (Table I). However, the contribution to LV filling volume by rapid diastolic filling (range 8 to 92%) was diminished in patients with HC and the contribution of atrial systole (range 5 to 89%) was increased (Table I, Fig. 3). LV filling during atrial systole was above the upper limit of normal of 31% in 17 patients (40%), including 13 patients whose peak filling rate was in the normal range (Fig. 4 and 5). Neither filling volume during rapid diastolic filling nor filling volume during atrial systole correlated with peak filling rate (r = 0.56 and 0.52, respectively). As previously reported,[7] time to peak filling rate in patients with HC (177 ± 38 ms) was significantly greater than normal (Table I) and was above the upper limit of normal of 180 ms in 24 patients (57%).

Effect of verapamil: Verapamil significantly reduced resting heart rate (Table I). Systolic blood pressure was reduced by verapamil (114 ± 25 mm Hg control, 109 ± 20 mm Hg with verapamil; p <0.05), but diastolic blood pressure was not altered (70 ± 12 mm Hg control, 66 ± 11 mm Hg with verapamil, difference not significant). LV ejection fraction was not changed by verapamil, but peak filling rate significantly increased and time to peak filling rate decreased (Table I), as previously described.[7]

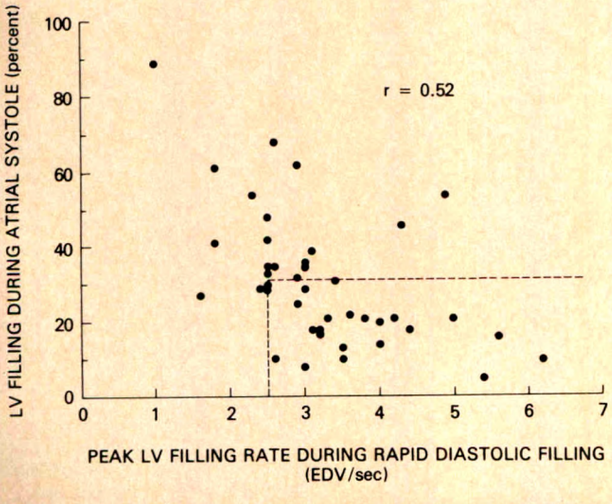

FIGURE 4. Left ventricular (LV) filling volume during atrial systole plotted as a function of peak rate of rapid diastolic filling. **Dashed lines** indicate the expected normal range. LV filling during atrial systole was above normal in 13 patients with normal peak LV filling rate.

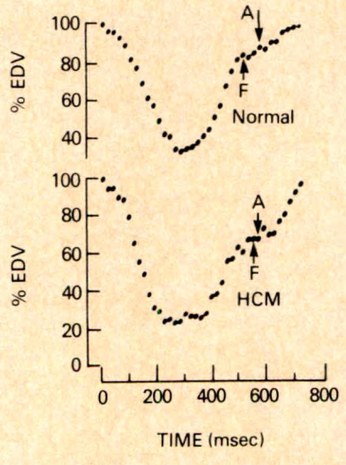

FIGURE 5. Left ventricular time-activity curves from a normal volunteer (**top**) and a patient with hypertrophic cardiomyopathy (HCM). Termination of rapid diastolic filling (F) and onset of atrial systole (A) are indicated. Heart rate (83 and 81 beats/min) and ejection fraction (68 and 73%) are similar. Peak rate of rapid diastolic filling is normal in each patient (4.4 and 3.1 EDV/s), but filling volume during rapid filling is reduced in the patient with hypertrophic cardiomyopathy (76 versus 61%) and filling volume during atrial systole is increased (18 versus 39%). EDV = end-diastolic volume.

TABLE II Variability of Radionuclide Measurements in 25 Patients

	Study I (Mean ± SD)	Study II (Mean ± SD)	Maximal Change Between Studies	Average Change Between Studies (Mean ± SD)
Heart rate (beats/min)	73 ± 12	72 ± 12	12	−0.9 ± 3.8
LV ejection fraction (%)	72 ± 11	72 ± 10	7	0.2 ± 2.4
LV diastolic filling				
Peak LV filling rate (EDV/s)	2.8 ± 1.1	2.9 ± 1.1	0.7	0.2 ± 0.23
Time to peak LV filling rate (ms)	192 ± 46	187 ± 42	56	−5.2 ± 24
LV filling volume during RDF (%)	66 ± 11	66 ± 12	11	0.1 ± 5.5
LV filling volume during AS (%)	38 ± 17	36 ± 17	12	−1.8 ± 4.9

SD = standard deviation. For other abbreviations, see Table I.

This change was associated with an increase in the contribution of rapid diastolic filling to LV filling volume, from 67 ± 17% to 83 ± 7% ($p < 0.001$), and a decrease in the contribution of atrial systole to LV filling, from 31 ± 18% to 16 ± 9% ($p < 0.001$) after verapamil (Table I, Fig. 6 and 7). LV filling volume during rapid diastolic filling was subnormal after verapamil in only 2 patients (5%), and filling volume during atrial systole was above normal in only 3 patients (7%).

Reproducibility of radionuclide measurements: In the 25 patients with HC who were studied twice with no medications, none of the variables describing LV diastolic filling changed between the 2 studies (Table II). The variations in ejection fraction, peak filling rate, and time to peak filling rate were similar to the error previously described for these parameters.[7] The average change between studies was 0.1 ± 5.5% for the percentage of filling volume during rapid diastolic filling and 1.8 ± 4.9% for the percentage of filling during atrial systole. Thus, in most patients (as well as in mean values), the changes induced by verapamil in relative filling during rapid filling and atrial systole were >2 standard deviations above the expected variability of the technique (Fig. 6). The correlation between study 1 and study 2 was $r = 0.96$ (SE = 5.05) for filling volume during rapid diastolic filling and $r = 0.89$ (SE = 5.16) for filling volume during atrial systole.

Discussion

Impaired diastolic filling of the hypertrophied left ventricle is a common manifestation of patients with HC[1,3–7] that contributes to the production of symptoms of pulmonary venous hypertension, reduced cardiac output, and possibly angina pectoris. Previous studies indicate that the timing of rapid diastolic filling is abnormal in such patients,[4,6,7] although the peak rate of rapid diastolic filling may be normal.[7] Despite the normal rate of rapid diastolic filling, our data indicate that the proportion of LV filling during rapid diastolic filling is reduced. Because LV stroke volume is directly related to LV end-diastolic volume in patients with HC,[21] reduced LV filling during early rapid diastolic filling would decrease LV end-diastolic volume and forward cardiac output, unless the contribution to LV filling by slow diastolic filling or atrial systole was augmented. In the current study, the percentage of LV filling during atrial systole in patients with HC was significantly greater than that in normal subjects. The contribution of atrial systole to LV filling was above the upper limit of normal in 40% of patients, including 36% of patients whose peak rate of rapid diastolic filling was within the normal range. These data support earlier echocardiographic observations that the volume of LV filling during rapid diastolic filling is reduced in such patients and that of atrial systole is increased.[6]

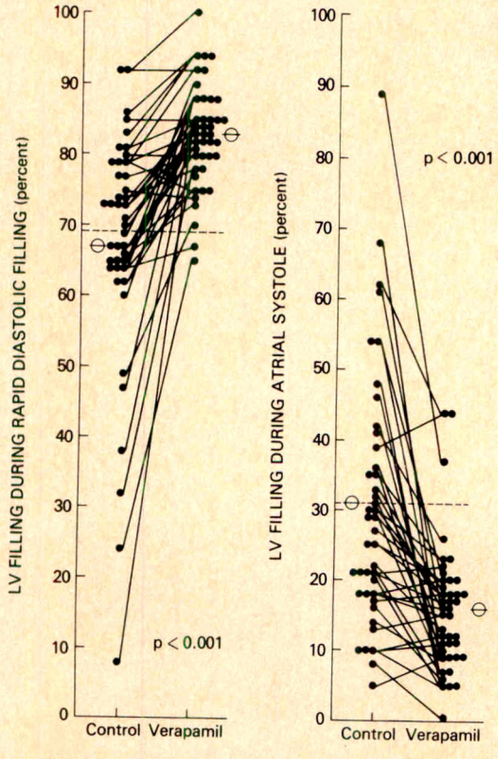

FIGURE 6. Left ventricular (LV) filling volume during rapid diastolic filling (**left**) and during atrial systole (**right**) before and after verapamil. Filling volumes are expressed as percent of LV stroke volume. **Dashed lines** indicate the lower limit of normal for filling during rapid diastolic filling (69%) and the upper limit of normal for filling during atrial systole (31%). **Open circles with bars** indicate mean values.

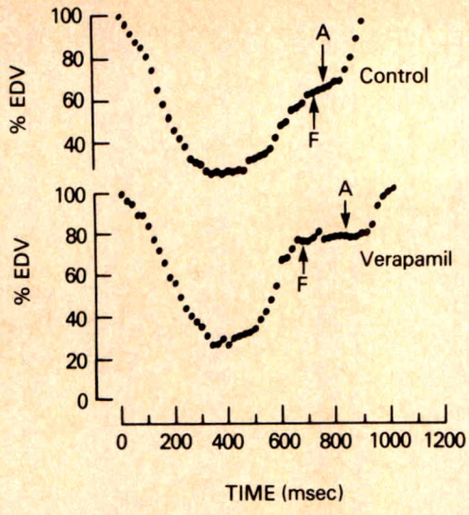

FIGURE 7. Time-activity curves obtained from a patient with hypertrophic cardiomyopathy before (control) and after verapamil. Ejection fraction was not significantly affected (75 to 72%). Increased rate of rapid diastolic filling after verapamil (from 1.8 to 3.4 EDV/s) is associated with increased contribution of rapid filling to ventricular filling volume (from 49 to 71%) and reduced contribution of atrial systole (from 41 to 26%). Termination of rapid filling (F) and onset of atrial systole (A) are indicated. EDV = end-diastolic volume.

Verapamil therapy reduces the time period of isovolumic relaxation and increases the time period of rapid diastolic filling.[11] The rate of rapid diastolic filling is increased by verapamil and the time from end-systole to the peak rate of rapid filling is decreased.[7] The results of the current investigation indicate that these changes are associated with a significant increase and, in many cases, normalization of the contribution of rapid diastolic filling to LV diastolic volume and a reduction in the contribution of atrial systole (Fig. 6 and 7).

In the absence of quantitative estimates of absolute LV volume (a limitation of our noninvasive technique), the abnormalities in LV filling during rapid filling and atrial systole, and the changes induced by verapamil, cannot be measured volumetrically and must be expressed relative to total stroke volume. However, previous studies of patients with HC indicate that intravenous administration of verapamil results in either no change or an increase in total stroke volume.[11,21,22] If these intravenous data pertain to the effects of oral verapamil therapy, then the changes we observed after verapamil in relative LV filling during the 2 phases of diastole would represent an increase in absolute LV volume contributed by rapid diastolic filling.

Our data have several potential clinical implications. Increased dependence on atrial systole to maintain adequate LV filling volumes for preservation of cardiac output places many patients with HC at risk of acute reduction in cardiac output with the loss of synchronized atrial contraction. Hence, atrial fibrillation, atrial flutter, and ventricular tachycardia, commonly encountered arrhythmias in these patients,[8–10] may precipitate acute, life-threatening hemodynamic decompensation. By increasing the relative magnitude of LV filling volume during early rapid diastolic filling and thereby diminishing the relative filling contribution of atrial systole, verapamil therapy may reduce the hemodynamic risks of any arrhythmia leading to the loss of the atrial contribution to LV filling.

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Regression of Myocardial Cellular Hypertrophy With Vasodilator Therapy in Chronic Congestive Heart Failure Associated With Idiopathic Dilated Cardiomyopathy

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Forty-nine patients with idiopathic dilated cardiomyopathy (IDC) were evaluated to determine the hemodynamic and morphologic effects of vasodilator therapy. Hydralazine (225 mg/day, H), isosorbide dinitrate (160 mg/day, I), and combination H + I therapy were compared with placebo (P) at baseline and after 3 months of continuous therapy. Thirty-three randomly assigned patients completed the study. Hemodynamic parameters included the echocardiographic percent change of left ventricular diameter (%ΔD), the systolic time intervals ratio of preejection period to left ventricular ejection time (PEP/LVET), the pulmonary capillary wedge pressure, mean pulmonary artery pressure, cardiac index, systemic vascular resistance, and pulmonary vascular resistance. An endomyocardial biopsy was performed at baseline and after 3 months; the myocardial cell diameter of 50 cells per biopsy was measured.

During the 3-month study 5 patients died; there was not a significant difference among the groups in the number of deaths. The %ΔD and PEP/LVET did not change in the P or I groups but did improve significantly from baseline in the H and H + I groups. The pulmonary capillary wedge and mean pulmonary artery pressures and the pulmonary vascular resistance did not change in the P or H groups but did decrease significantly in the I and H + I groups. The P and I groups did not have improvement in systemic vascular resistance or cardiac index, whereas the H group had a decrease in systemic vascular resistance and an increase in cardiac index from 2.5 ± 0.4 to 3.1 ± 0.4 liters/min/m² ($p < 0.05$). The H + I group also had a decrease in systemic vascular resistance; the cardiac index increased from 2.3 ± 0.4 to 3.1 ± 0.4 liters/min/m² ($p < 0.01$). Myocardial cell diameter did not change in the P or I group. Cell diameter of the H group decreased from 25.4 ± 3.1 μm at baseline to 23.1 ± 3.8 μm ($p < 0.05$) after 3 months of continuous therapy. The H + I group decreased its cell diameter from 23.9 ± 3.7 to 22.2 ± 2.2 μm ($p < 0.05$).

Compared with P and H, patients treated with I alone or H + I had a significant reduction of preload. In contrast to P and I, H alone and H + I elicited improvement in parameters of inotropy and afterload, and this improvement was accompanied by a reduction in cell diameter. Chronic therapy of heart failure with H and H + I effects a persistent augmentation of cardiac function and improvement of myocardial cellular morphology.

Vasodilator therapy is now an accepted method of managing patients who have congestive heart failure that remains refractory to digitalis and diuretics.[1–3] Such congestive heart failure is usually characterized by an elevated preload or afterload, or both; a popular vasodilator regimen employs isosorbide dinitrate (a preload-reducing agent) or hydralazine (an afterload-reducing agent), or both.[4] Although this combination improves resting hemodynamic function[4,5] and augments exercise performance both immediately[6–9] and during long-term therapy,[10–12] its effect on myocardial morphology has not been studied. This study assesses the effects of oral isosorbide dinitrate, hydralazine, and the combination of the 2 on the myocardial cell size of patients with chronic, severe congestive heart failure secondary to idiopathic dilated cardiomyopathy (IDC).

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Methods

Patients eligible for this study had diagnostic catheterization for determination of pressures, function, and coronary anatomy. Qualifying characteristics of the patients for the

study included left ventricular end-diastolic pressure >10 mm Hg, an angiographic ejection fraction <50%, and no narrowings >50% in diameter in any coronary artery. Exclusion criteria included an alcohol intake >1 drink per day over the 2 months before study and myocarditis by endomyocardial biopsy.

Forty-nine subjects, 37 men and 12 women, entered the study. The average age was 57 ± 10 years (mean ± standard deviation [SD]). The symptoms of this group included dyspnea on exertion in all 49, easy fatigability in 10, peripheral edema in 9, angina-like chest pain in 10, and palpitations in 6. Duration of symptoms ranged from 1 to 120 months. Three were classified as New York Heart Association functional class II, 34 as functional class III, and 12 as functional class IV. The catheterization data revealed an average angiographic ejection fraction of 27 ± 9%, the average cardiac index was 2.4 ± 0.6 liters/min/m^2, and the average pulmonary capillary wedge pressure was 21 ± 8 mm Hg. Twenty-six patients had some degree of mitral regurgitation; 6 had tricuspid regurgitation. The cause of the congestive cardiomyopathy included an idiopathic etiology in 31, remote alcohol abuse in 16, and cardiomyopathy associated with the peripartal period and family history in 1 each. All patients were on maintenance doses of digitalis and diuretics; antiarrhythmic and anticoagulant medications were employed when indicated. The digitalis, diuretic, and antiarrhythmic medications were maintained at the same dosage level over the 3 months of the study.

Invasive and noninvasive testing: All patients had endomyocardial biopsy through the right internal jugular vein.[13] The tissue removed from the right side of the interventricular septum was immediately submerged in cold 2% glutaraldehyde and reserved for analysis. The internal jugular site was then used for placement of a triple-lumen, flow-directed catheter positioned in the pulmonary artery. This catheter provided measurement of the pulmonary artery and pulmonary capillary wedge pressures and cardiac output; pressures were determined with Electronics for Medicine M2101 pressure amplification units and cardiac outputs by thermodilution using an Instrumentation Laboratory 601 computer and 602 recorder. Systemic blood pressure was recorded indirectly with a calibrated sphygmomanometer. Systemic vascular resistance was calculated from the formula: systemic vascular resistance = mean systemic arterial pressure × 80/cardiac output. Pulmonary vascular resistance was obtained by the formula: pulmonary vascular resistance = mean pulmonary artery pressure × 80/cardiac output.

Echocardiograms were performed with an Echo IV ultrasonoscope and an Electronics for Medicine recorder. A single echocardiographic technician performed echocardiography using identical techniques and transducer placement for each study. Blinded echocardiographic interpretation was performed by 1 of us (DVU) in accordance with the recommendations of the American Society of Echocardiography.[14] The fractional shortening of the minor axis of the left ventricle with systole (%ΔD) was used as the echocardiographic determinant of left ventricular function. Systolic time intervals were obtained with an Electronics for Medicine unit using the specifications previously outlined.[15] The preejection period (PEP) to left ventricular ejection time (LVET) ratio was used as the measure of left ventricular performance. A single technician was used to perform this test. The reproducibility of these tests has previously been determined in our laboratory.[16]

Drug testing: Measurements included systemic blood pressure, heart rate, pulmonary artery pressure, pulmonary capillary wedge pressure, systemic vascular resistance, pulmonary vascular resistance, cardiac output, echocardiographic %ΔD, and the systolic time intervals PEP/LVET. Measurements were made at baseline and repeated 30 minutes and 1, 2, 3, 4, and 5 hours after drug administration. Oral isosorbide dinitrate (I) (40 mg), oral hydralazine (H) (1 mg/kg), or a combination of the 2 (H + I) was administered on successive days to establish that no adverse reaction would occur with these drug regimens. The patients were then randomly assigned to 1 of 4 treatment groups. The first group received placebo (P) (4 times a day), the second group received I (160 mg/day in 4 divided doses), the third group received H (3 mg/kg/day in 3 divided doses), and the last group received a combination of H + I in the same doses just mentioned. Patients were blinded to their treatment group.

Follow-up studies: Patients returned monthly in the ensuing 3 months for clinical evaluation and pill counts. After 3 months of therapy, the patients were readmitted and underwent repeat endomyocardial biopsy and repositioning of the triple-lumen, flow-directed catheter. The patients had repeat hemodynamic and noninvasive tests 30 minutes and 1, 2, 3, 4, and 5 hours after taking their assigned drug regimen (P, I, H, or H + I).

Analysis of biopsy tissue: This laboratory has performed over 600 endomyocardial biopsy procedures. At least 2 pieces of tissue from each procedure are reserved for histologic analysis. Various fixative and staining procedures have been used to determine which technique presents the least artifact. In our laboratory, the best histologic preservation and the most reproducible results occur when the tissue is >1 mm^3 and immediately placed in cold buffered 2% glutaraldehyde. This finding is similar to that of Thomsen and Torp[17] but differs from the recommendation of Fenoglio.[18] The tissue is kept in buffered glutaraldehyde for precisely 4 hours after which it is transferred to phosphate buffer.

The tissue from each biopsy procedure in this study measured 1 to 2 mm^3 and weighed 1 to 4 mg. Tissue was placed in 2% buffered glutaraldehyde (pH 7.35) within 12 seconds of closure of the jaws of the bioptome on the right ventricular septal myocardium. Light microscopic slides 3 to 5 μm in thickness were prepared from paraffin-embedded sections. The slides were stained by routine hematoxylin and eosin by the method of Sheehan and Hrapchak.[19] The myocardial slices were examined through a 43× objective lens and a 10× eyepiece with an ocular micrometer disc. The diameter of a myocardial cell was determined by measuring the distance across the cell at its most narrow plane across the nucleus (Fig. 1) according to the technique previously described by Baandrup and Olsen[20] and as previously reported by our laboratory. At least 50 cells from each biopsy were measured and their diameters averaged to determine the value for each patient.

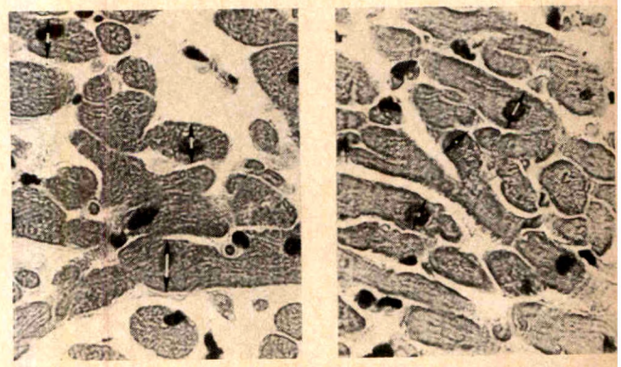

FIGURE 1. Hematoxylin and eosin stain of endomyocardial biopsy specimens from a patient who received hydralazine and isosorbide dinitrate. **Left,** pretreatment biopsy; **right,** after 3 months of therapy. (Magnification ×450, reduced 43%.)

The microscopist was blinded to the treatment group and to the time of the biopsy. The difference of the means on repeated measurements of the biopsies was <5%.

Analysis of data: The peak effect of the patients' drug regimen after 3 months of therapy was compared with the average baseline measurements before the start of the study by the paired *t* test. The myocardial cell size in each group was compared from the baseline to that at 3 months of therapy by the paired *t* test. The change in each of these tests from baseline was compared between the groups by unpaired Student's *t* test. In addition, linear regression analysis was used to correlate changes in individual and group myocardial cellular diameters with changes in pulmonary capillary wedge pressure, cardiac index, systemic vascular resistance, and pulmonary vascular resistance.

Results

After 3 months of continuous treatment, 33 patients returned for follow-up study. Sixteen patients did not complete the study because of death in 5 patients, resumption of alcohol use in 2, change of residence in 3, technical problems with biopsy or catheter in 1, and refusal to repeat study in 5. The deaths by group were P, 0 deaths; I, 3; H, 1; and H + I, 1 (difference among groups not significant [NS]). Four of the 5 deaths were sudden, presumably from arrhythmias, although none of these was documented by monitoring at the time of death. One patient died from pneumonia at her local hospital. No patient withdrew from the study because of intolerable side effects, although several patients complained of severe headaches early in the study which dissipated with time.

The 33 patients who completed the study were assigned to the following groups: P, 11 patients; I, 6; H, 9; and H + H, 7. Table I shows the baseline and post-therapy value for the 33 subjects who completed the study. The baseline mean ± 1 SD is tabulated for each

TABLE I Symptomatic, Hemodynamic, and Morphologic Changes With Therapy

	FC		PEP/LVET		%ΔD		PCW		Cardiac Index (L/min/m²)		Cell D	
Group	B	P-Tx	B	P-Tx	B	P-Tx	B	P-Tx	B	P-Tx	B	P-Tx
Placebo												
P-1	3	2	0.60	0.64	12	14	12	6	2.7	3.4	20.5	21.5
P-2	3	2.5	0.65	0.68	15	15	23	15	1.6	1.6	18.9	18.2
P-3	3	2	0.61	0.62	18	17	11	12	2.4	2.2	25.5	24.4
P-4	3	2	0.45	0.47	13	19	38	28	2.2	2.9	21.6	25.6
P-5	3	3	0.55	0.58	18	19	26	21	2.3	2.6	18.6	20.5
P-6	3	2.5	0.54	0.50	18	17	25	26	2.6	2.6	20.3	18.5
P-7	3	3	0.50	0.55	23	20	10	10	2.8	2.1	23.8	20.2
P-8	4	4	0.67	0.68	9	9	14	29	1.7	1.4	21.8	24.9
P-9	3.5	3	0.51	0.42	15	17	23	16	2.8	3.7	27.9	26.6
P-10	3	3	0.84	0.79	19	24	29	31	2.8	2.5	22.6	24.3
P-11	3	3	0.66	0.68	14	11	11	12	2.4	2.4	21.8	20.3
Mean±SD	3.1±0.3	2.7±0.6	0.60±0.11	0.58±0.12	16±4	17±4	20±9	19±9	2.4±0.4	2.5±0.7	22.1±3.8	22.3±3.4
Isosorbide												
I-1	3	2	0.51	0.50	17	23	12	12	3.0	3.0	22.2	23.7
I-2	3	3	0.81	0.85	7	13	18	13	2.4	2.1	25.1	24.9
I-3	3	2	0.57	0.62	11	14	11	3	2.8	2.2	24.7	24.2
I-4	3	2	0.61	0.75	9	11	19	12	3.0	2.5	19.2	19.3
I-5	3	2.5	0.59	0.68	13	12	18	14	2.9	2.6	22.2	21.4
I-6	4	4	0.89	0.82	12	13	36	25	1.1	2.1	24.2	25.6
Mean±SD	3.2±0.4	2.6±0.8	0.66±0.15	0.70±0.13	12±3	14±4	19±9	13±7	2.5±0.7	2.4±0.4	22.9±2.2	23.1±2.4
Hydralazine												
H-1	4	3	0.67	0.62	TI		20	30	2.3	2.9	31.7	30.8
H-2	2	2	0.90	0.72	10	17	10	11	2.5	3.8	25.8	25.3
H-3	2.5	2	0.75	0.51	14	20	24	24	3.0	3.3	28.3	26.5
H-4	3	2.5	0.71	0.51	13	17	25	23	2.4	2.3	23.8	21.0
H-5	3	2	0.59	0.57	TI		14	16	2.8	3.2	25.5	20.9
H-6	3	2.5	0.64	0.70	18	19	18	16	2.5	3.0	24.1	22.2
H-7	3	2.5	0.50	0.52	26	32	22	17	2.4	3.1	22.3	19.8
H-8	4	3	0.55	0.49	17	29	15	17	2.1	2.9	21.5	18.5
H-9	3	2	0.69	0.52	16	24	20	16	2.7	3.2	25.6	22.4
Mean±SD	3.1±0.6	2.4±0.4	0.67±0.12	0.57±0.09	16±5	23±6	19±6	19±7	2.5±0.4	3.1±0.4	25.4±3.1	23.1±3.8
Hydralazine + Isosorbide												
H+I-1	4	3	0.72	0.66	16	18	27	15	2.0	3.3	29.8	26.6
H+I-2	3	3	0.79	0.79	12	14	20	16	2.9	3.2	27.5	22.8
H+I-3	3	2	0.63	0.48	12	24	19	12	2.4	2.9	24.8	21.0
H+I-4	3	2	0.83	0.75	15	16	27	22	2.4	3.0	19.5	19.1
H+I-5	3	2.5	0.62	0.54	17	23	22	22	2.2	3.3	20.1	20.6
H+I-6	3	2	0.64	0.44	12	14	18	16	1.8	2.9	22.8	22.4
H+I-7	3.5	3	0.63	0.46	15	20	30	13	2.3	3.2	23.5	23.1
Mean±SD	3.2±0.4	2.5±0.5	0.69±0.09	0.58±0.13	14±2	19±4	23±5	16±4	2.3±0.4	3.1±0.4	23.9±3.7	22.2±2.2

B = baseline; Cell D = cell diameter (μm); FC = functional class; P-Tx = observations after 3 months of continuous therapy; PCW = pulmonary capillary wedge pressure (mm Hg); PEP/LVET = preejection period to left ventricular ejection time by systolic time intervals; SD = standard deviation; TI = technical inadequate echocardiogram; %ΔD = percent change of the minor axis of the left ventricle with systole by echocardiography.

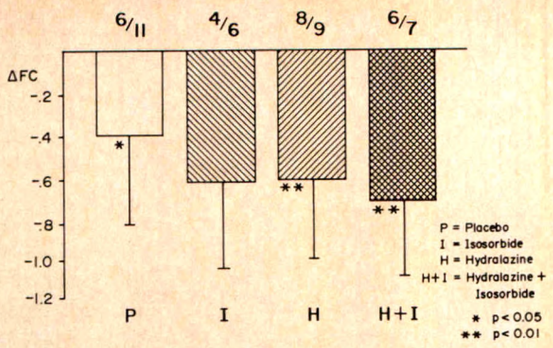

FIGURE 2. Mean change ± SD in functional class (ΔFC) from baseline to 3 months of therapy for each group. All 4 groups reported significant improvement. The fractions at the top represent the number of patients improved over the total number in that group who completed the study.

test for each group. No significant differences existed at baseline among the groups for any of these characteristics.

After 3 months of continuous therapy and while still on therapy, a significant improvement in functional class was noted in all groups (Fig. 2). Improvement was noted in 6 of the 11 patients receiving P, in 4 of 6 receiving I, in 8 of 9 receiving H, and in 6 of 7 receiving H + I.

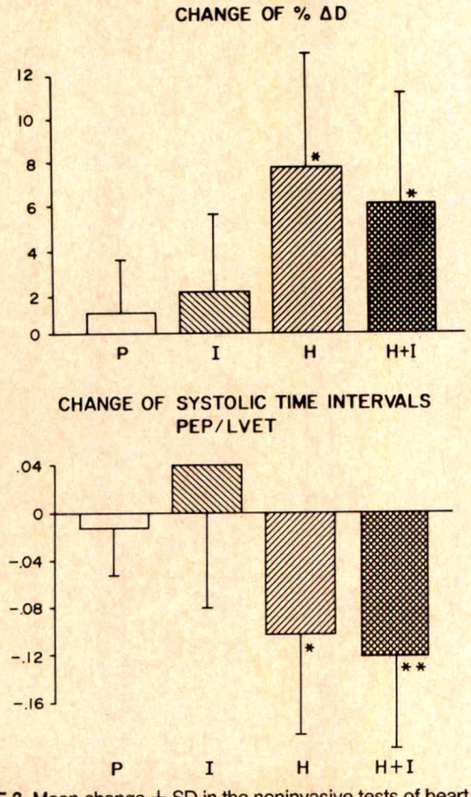

FIGURE 3. Mean change ± SD in the noninvasive tests of heart function for each group. The H and H + I groups had an improved % ΔD (* $p < 0.05$) from baseline to 3 months of therapy. The H and H + I groups also had improvement in the preejection period to left ventricular ejection time ratio (PEP/LVET) of the systolic time intervals (* $p < 0.05$, ** $p < 0.01$).

The change from baseline of the noninvasive tests of left ventricular function is shown in Figure 3. The %ΔD did not change in the P or I group, but did improve from 16 ± 5% ($\bar{X}$ ± SD) to 23 ± 6% ($p < 0.05$) in the H group and from 14 ± 2% to 19 ± 4% ($p < 0.05$) in the H + I group. The PEP/LVET also did not change in the P or I group. The H group had a decrease in PEP/LVET from 0.67 ± 0.12 to 0.57 ± 0.09 ($p < 0.05$). The H + I group had a decrease in PEP/LVET from 0.69 ± 0.09

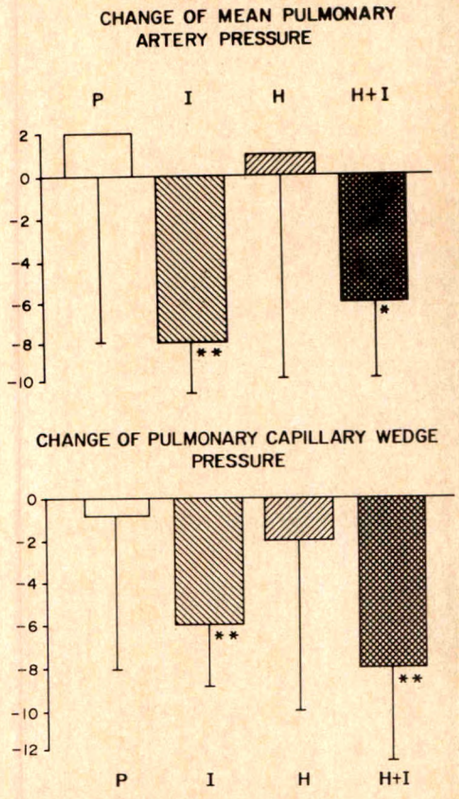

FIGURE 4. The **vertical axis** shows the mean change (mm Hg) ± standard deviation from baseline to 3 months of therapy for each group. The I and H + I groups had a significant decrease in mean pulmonary artery pressure and pulmonary capillary wedge pressure (* $p < 0.05$, ** $p < 0.01$), whereas the P and H groups did not change.

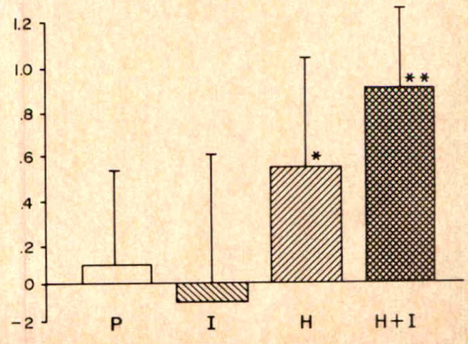

FIGURE 5. The **vertical axis** shows the change in cardiac index (in liters/min/m^2) from baseline. The P and I groups demonstrated no change. The H and H + I groups had an increase in cardiac index (* $p < 0.05$, ** $p < 0.01$).

to 0.58 ± 0.13 ($p < 0.01$). There was no difference among the groups for the changes from baseline in either %ΔD or PEP/LVET.

Changes in mean pulmonary artery and pulmonary capillary wedge pressures are shown in Figure 4. Neither pulmonary artery nor pulmonary capillary wedge pressure changed from baseline in the P or H group. The I group had a decrease in mean pulmonary artery pressure from 28 ± 9 mm Hg at baseline to 20 ± 9 mm Hg ($p < 0.01$) during treatment and in pulmonary capillary wedge pressure from 19 ± 9 to 13 ± 7 mm Hg ($p < 0.01$). The H + I group also demonstrated a significant decrease in mean pulmonary artery pressure from 33 ± 4 to 27 ± 4 mm Hg ($p < 0.05$) and in pulmonary capillary wedge pressure from 23 ± 5 to 16 ± 4 mm Hg ($p < 0.01$). There was no significant difference among the groups in these changes.

The change in cardiac index from baseline is shown in Figure 5. Neither the P nor the I group demonstrated an improvement in cardiac index, whereas the H and H + I groups did. The H group had an increase in cardiac index from 2.5 ± 0.4 to 3.1 ± 0.4 liters/min/m^2 ($p < 0.05$). The H + I group had an increase in cardiac index from 2.3 ± 0.4 to 3.1 ± 0.4 liters/min/m^2 ($p < 0.01$). There was no significant difference between the groups in these changes.

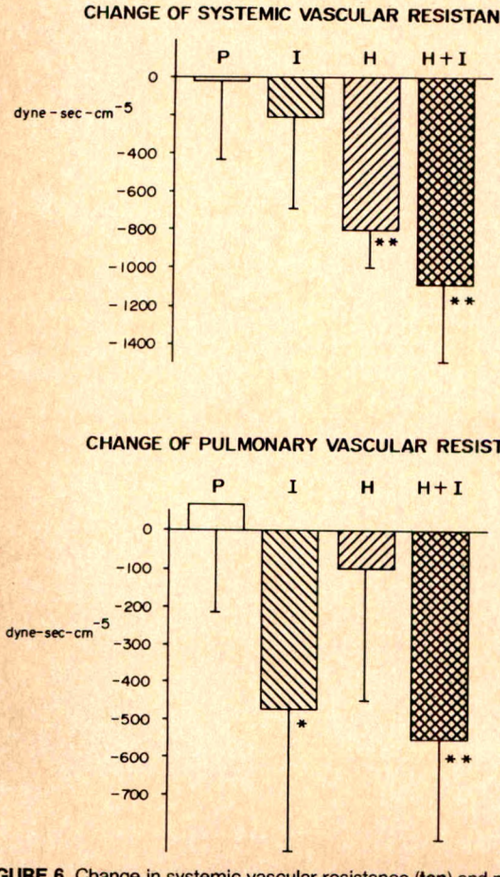

FIGURE 6. Change in systemic vascular resistance (**top**) and pulmonary vascular resistance (**bottom**) from baseline to after 3 months of therapy (* $p < 0.05$, ** $p < 0.01$).

Changes in vascular resistance from baseline are shown in Figure 6. There was no significant difference among the groups at baseline for the systemic or pulmonary vascular resistances. The P group did not have a change in systemic or pulmonary vascular resistance. The I group did not have a change in systemic vascular resistance from baseline; however, its pulmonary vascular resistance decreased from 691 ± 423 dynes s cm^{-5} at baseline to 308 ± 213 dynes s cm^{-5} ($p < 0.05$) after 3 months of therapy. The H group did not have a change in pulmonary vascular resistance, but the systemic vascular resistance decreased from 2,084 ± 484 to 1,442 ± 424 dynes s cm^{-5} ($p < 0.01$). Both systemic vascular resistance (2,235 ± 445 to 1,360 ± 306 dynes s cm^{-5}, $p < 0.01$) and pulmonary vascular resistance (723 ± 236 to 297 ± 131 dynes s cm^{-5}, $p < 0.01$) decreased in the H + I group.

Myocardial cell diameter (Fig. 7) did not change in the P or I group. Cell diameter in the H group decreased from 25.4 ± 3.1 μm at baseline to 23.1 ± 3.8 μm ($p < 0.01$) after 3 months of continuous therapy. The H + I group had a decrease in cell diameter from 23.9 ± 3.7 to 22.2 ± 2.2 μm ($p < 0.05$). There was no significant difference between the groups in these changes.

Changes in myocardial cell diameter in individual patients did not correlate with changes in pulmonary capillary wedge pressure, cardiac index, systemic vascular resistance, or pulmonary vascular resistance. There was a correlation of the changes in cell diameter of group means with cardiac index ($r = 0.86$) and systemic vascular resistance ($r = 0.87$). The change in cell diameter did not correlate with changes in pulmonary capillary wedge pressure or pulmonary vascular resistance.

Discussion

Clinical response: This study demonstrated that I-containing drug regimens resulted in a persistent decrease in preload as shown by the decreased pulmonary capillary wedge pressure. Hydralazine-containing regimens resulted in a persistent improvement in systolic function as demonstrated by an improved echocardiographic %ΔD, systolic time intervals PEP/LVET, and cardiac index. In addition, symptomatic improvement was impressive. Not only did treated patients feel better, but 6 of 11 patients receiving placebo reported

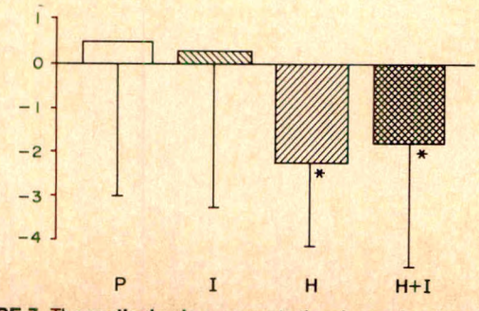

FIGURE 7. The **vertical axis** represents the change in micrometers of the myocardial cell diameter from baseline to 3 months of therapy. The decrease in cell size was significant in the H and H + I groups.

some functional improvement despite an absence in hemodynamic response. Improved functional class in the placebo group may reflect significant motivational factors or subtle changes in general care, or both, with close follow-up over the 3-month period.

Tolerance: Significant diminution in response with chronic therapy (tolerance) did not develop with either agent. Tolerance to I is controversial.[22–24] Thadani et al[22] showed that plasma I levels are not decreased during chronic therapy but that end-organ responsiveness is decreased. Lee et al[24] demonstrated that resting and exercise hemodynamic response in their patients was maintained 1 month. A loss of responsiveness to I after 3 months of therapy was not observed in our study.

A long-term H study has demonstrated tolerance to this agent in 11% of patients after an average of 37 weeks of therapy.[25] The patient group displaying H tolerance retained responsiveness to intravenous nitroprusside and other oral vasodilators.[25] Of the 16 patients on H or H + I who completed our 3-month study, all demonstrated continued hemodynamic responsiveness. Therefore, resting invasive and noninvasive tests did not demonstrate tolerance to I or H in this study.

Deaths: Five patients died during the 3-month course of study, 4 from sudden death and 1 from pneumonia. One patient who died suddenly showed no evidence of emboli on postmortem examination. He presumably died from an arrhythmia. Sudden death is consistent with previous reports which suggest that cardiomyopathic patients die more commonly from arrhythmias and emboli than from refractory heart failure.[26–29] The 4 sudden deaths were divided among the 3 treatment groups; no deaths occurred in the placebo group. Statistical significance was not achieved for the incidence of death among the groups.

Measurements of myocardial cell size: The unique aspect of this study was the documentation that myocardial cell size decreased with therapy. However, several problems interfere with the interpretation of these results. The techniques employed for cell sizing have been studied in our laboratory and the present methods appear to be best suited for our purposes. The techniques are precisely replicated with each biopsy and the reproducibility has been documented (<5% error on repeated measures). However, it is impossible to determine how closely our measurements mimic in vivo cell diameter.

A second problem is that of right versus left heart biopsy. The tissue for this study was removed from the right side of the interventricular septum and yet the changes in cell size correlated with the changes in systemic vascular resistance ($r = 0.87$) and not pulmonary vascular resistance ($r = 0.18$). A previous study demonstrated the similarity of cellular morphology of biopsy specimens from the left and right ventricle.[20] However, that study did not include quantitative cell sizing. Our study cannot resolve the question of the pertinence of left versus right heart biopsy, but it would appear that right ventricular endomyocardial biopsies are sufficient to explore some important morphologic changes in IDC.

Regression of hypertrophy: The myocardial cell diameter of the study patients was 23.2 ± 2.6 μm at baseline (normal 16 to 20 μm, unpublished observation from our laboratory). Animal models clearly demonstrated that hypertrophy is associated with increased afterload,[30] increased preload,[31] and intermittent hypoxia.[32] All 3 factors may have played a role in inducing cell growth in the study patients. Increased preload and afterload were documented at catheterization, and coronary blood flow studies in similar patients demonstrated decreased flow per gram of myocardium.[33,34]

Hypertrophy regressed toward normal groups that had H as part of their therapy. Reduction of a pressure load in animal models (release of an aortic band)[35] and in human subjects (aortic valve replacement for aortic valve disease[36] or treatment of hypertension)[37] leads to a regression of hypertrophy. Hydralazine not only reduces afterload but also increases coronary blood flow to a greater degree than the increase in myocardial oxygen demand.[38] Thus, H may have been successful in reducing cell size for these reasons.

The decrease in myocardial cell size is potentially important because (1) hypertrophied myocardial cells have depressed contractility, and (2) hypertrophied myocardium is less efficient. Factors that determine the course of hypertrophy and its effect on contractility are a combination of: the degree of wall stress, the duration of stress, the nature of the inciting stimulus, and the age and health of the subject.[39,40] A gradual progression in hypertrophy in a young animal does not depress contractility.[41] Sudden stress of a load on an older ventricle leads to pathologic hypertrophy and a depression of contractility.[39,42] Depressed contractility may be due at least partially to decreased enzyme activity, especially myosin ATPase.[43–47]

The hypertrophied myocardium is less efficient. With hypertrophy the intercapillary distance increases[48] and the capillary density decreases[49] with a resultant relative hypoxia of parts of the cell.[50] Within the cell, the mitochondrial to myofibrillar ratio decreases[51,52] and the ATP concentration decreases.[53] In addition, for each ATP consumed there is less tension produced.[54] Thus, the hypertrophied myocardium is unable to fully oxygenate its cells, less ATP is produced, and less force is generated.

The regression of hypertrophy is potentially beneficial to the patient by the reduction in intercapillary distance and the increase in capillary density. Some abnormalities of the myocardial cells are reversed (such as RNA content); others are not (hydroxyproline content).[35] Whether these improvements will be translated into long-term improved myocardial function or decreased mortality has not been determined. Further experience with vasodilators and long-term studies may help answer these questions.

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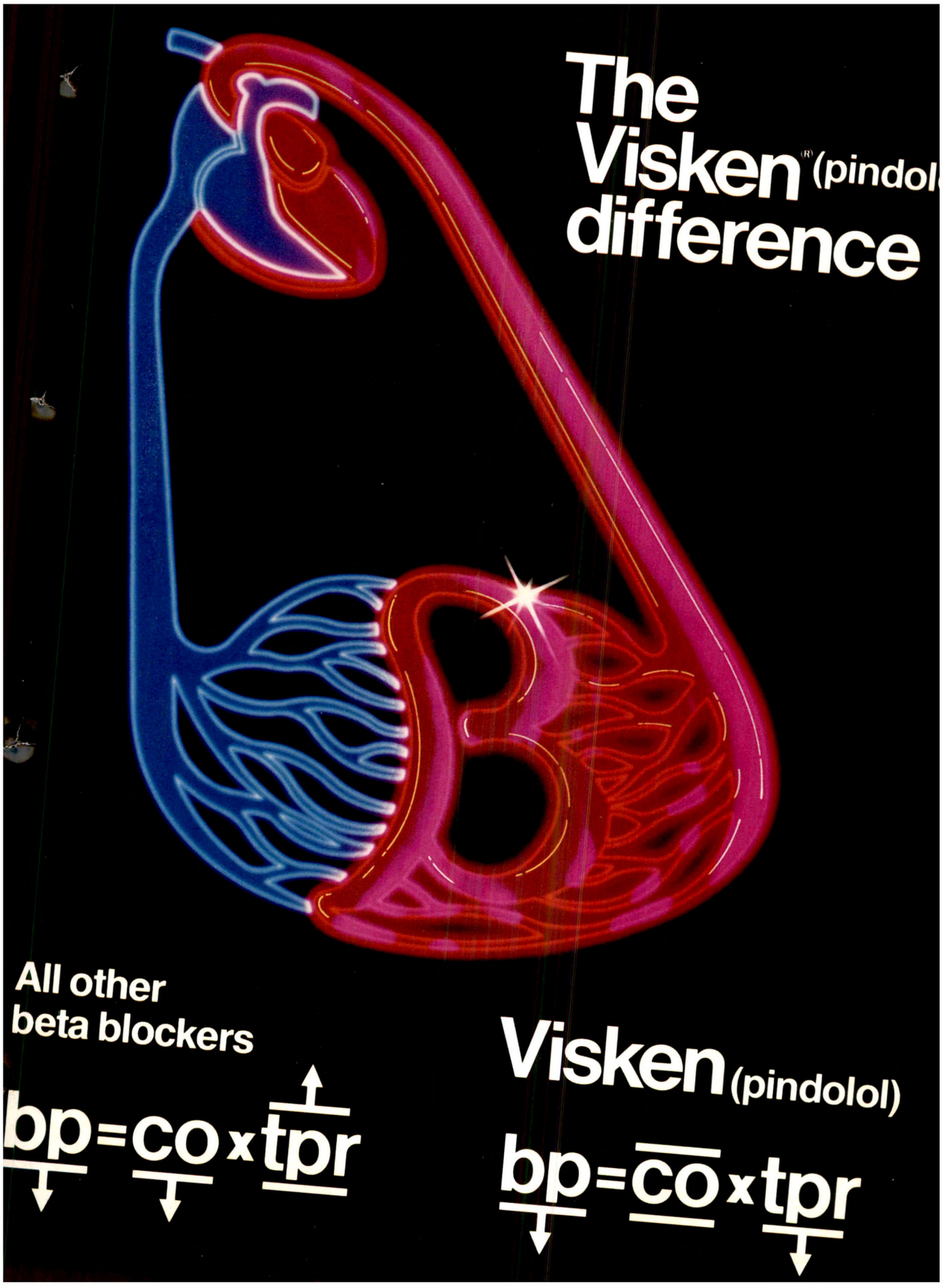
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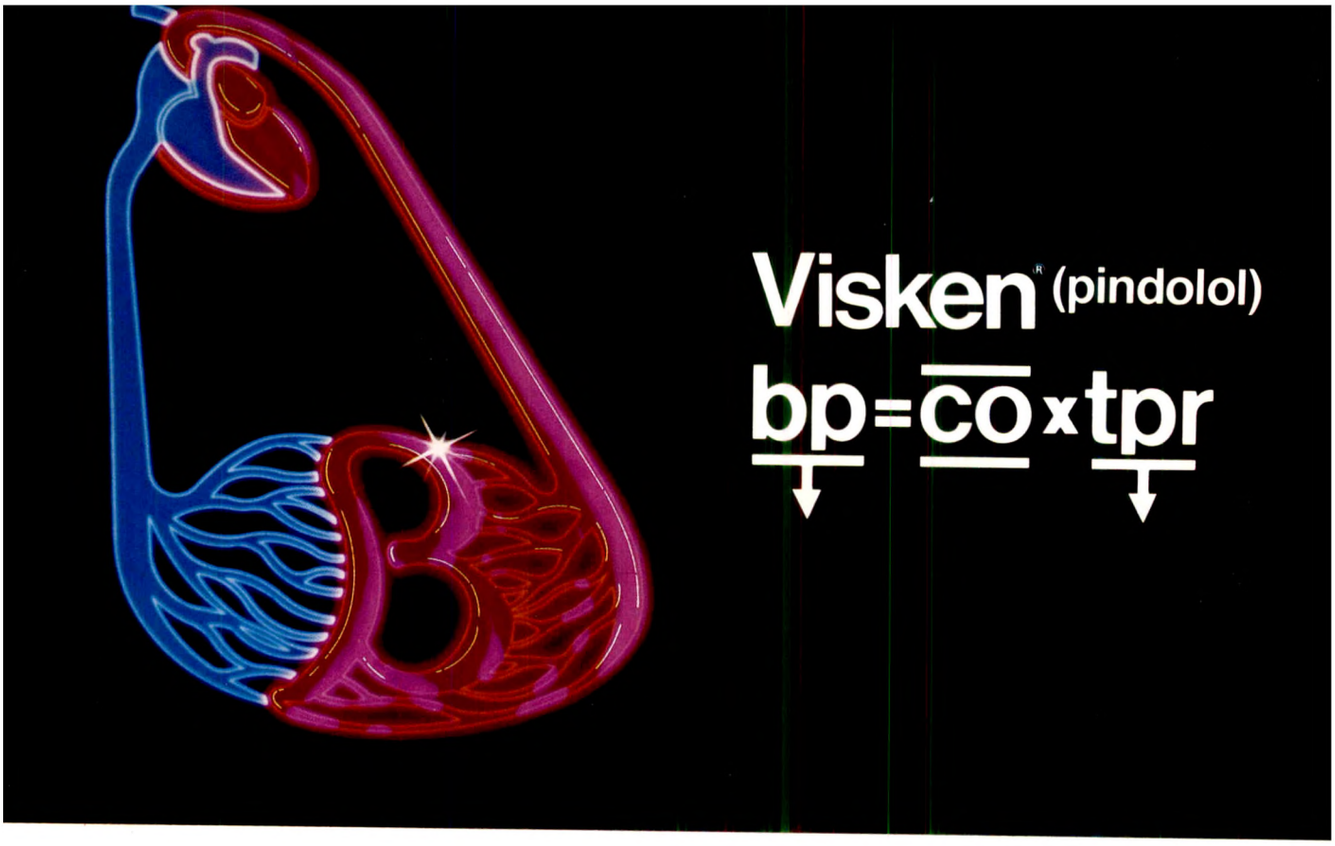

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raphy.[5,10,11] The cause of this disparity is speculative; however, it may represent a loss in sensitivity of edge detection caused by the lesser density differential between the diluted opacified blood nearest the endocardium in comparison with the soft tissue density of myocardial muscle. It is possible that this can be overcome by utilizing densitometric techniques and automated edge detection techniques.[13,14]

One of the major adverse reactions to contrast medium given intravascularly (or intracardiac) is arrhythmias.[15–18] The patients deemed most at risk in these noncontrolled studies are older male patients who were presumed to have coronary artery disease. Indeed, arrhythmias are not infrequent in patients with coronary artery disease undergoing left ventriculography and coronary angiography.[19]

In the current study, the incidence of ventricular ectopy was smaller after digital intravenous angiography than after direct left ventriculography. The absence of ventricular ectopy with the digital technique may be in part due to mechanical factors: the recoil of the left ventricular catheter serves as an endocardial irritant. An additional advantage of digital intravenous angiography is homogeneous opacification of the ventricle compared with the streaming of contrast medium with poor mixing inherent in direct left ventriculography. Regardless of electrophysiologic concerns, the absence of ventricular ectopic beats during peak left ventricular opacification decreases the possibility of a study on which quantitative analysis is precluded.

Digital subtraction and other contrast enhancement techniques can also be used after pulmonary arterial injection or direct left ventricular injection[10,20] with smaller volumes of contrast medium in order to diminish the hemodynamic and toxic side effects of contrast medium. Adequate visualization of the left ventricle with smaller volumes of contrast medium enables the utilization of multiple injections during the monitoring of physiologic and potential therapeutic interventions.

The important technical factors leading to inadequate digital fluoroscopic studies is motion of background structures in the region-of-interest caused by movement of the patient, respiratory activity, and coughing. In some instances when motion occurred between noncontrast and contrast images, another mask could be formed from fluoroscopy obtained after contrast medium had cleared from the left ventricle. Videotape recording of all fluoroscopic data from several seconds preceding the intravenous injection of contrast medium until contrast media had cleared from the left ventricle provided additional choices for mask images during postprocessing of the data.

In order to digitize the left ventricular images at a high framing rate (30 frames/second), a relatively coarse image matrix was used (128 × 128 pixels). For a large structure such as the left ventricle, this matrix density proved adequate as demonstrated by the good correlation between digital fluoroscopic and direct left ventricular estimates of volumes. On the other hand, adequate resolution of much smaller peripheral vessels containing a considerably lower concentration of contrast medium requires a greater matrix density.[1,2]

Compared with the relatively high radiation dose associated with pulsed X-ray exposures needed for digital fluoroscopy of peripheral vessels,[1,2,4] the technique used for digital intravenous ventriculography involved continuous fluoroscopy with radiation exposures (4.5 to 9.0 mA) only slightly greater than those used for standard fluoroscopy. Moreover, the technique used in the current study whereby fluoroscopic data were recorded on videotape and subsequently digitized into the image processing computer extends these types of studies to remote fluoroscopic facilities such as the coronary care unit.

Digital intravenous ventriculography offers several advantages over direct ventriculography: it provides adequate opacification of the ventricle without arrhythmias during the period of opacification; avoidance of arterial catheterization renders it an outpatient examination; and homogeneous opacification of the ventricle facilitates the application of automated programs for quantitation of segmental left ventricular contraction.

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Regional Distribution of Pulmonary Blood Volume: An Index of Pulmonary Capillary Wedge Pressure Determined From Blood Pool Scintigraphy

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Progressive redistribution of pulmonary blood flow to the lung apices occurs with increasing degrees of left ventricular failure, and correlates with increasing pulmonary capillary wedge pressure (PCWP). If similar changes in pulmonary blood volume (PBV) occur, then technetium-99m equilibrium blood pool scintigraphy, by assessing relative distribution of PBV, may allow prediction of PCWP. Therefore 30 patients being monitored with pulmonary artery balloon flotation catheters underwent imaging. PCWP was compared with the average radioactive count density arising from apical (A) and basal (B) regions of interest within the right lung, expressed as an A/B ratio. Correlation was strong for patients imaged erect, either posteriorly (r = 0.864, p = 0.001) or in the 45° left anterior oblique position (r = 0.842, p = 0.001), and only slightly less impressive for patients imaged supine (r = 0.678, p = 0.001). Especially when imaging was performed with patients erect, an A/B ratio greater than unity identified with high sensitivity (100%) and specificity (83 to 88%) an abnormally elevated PCWP (>12 mm Hg). Moreover, directional changes in the A/B ratio reflected concomitant changes in PCWP after intervention. Thus, analysis of lung A/B radioactive count ratios obtained by equilibrium blood pool scintigraphy may be used to evaluate PCWP.

Since the initial description of the assessment of pulmonary capillary wedge pressure (PCWP) by means of a flow directed balloon-tipped catheter,[1] years of clinical application have established the importance of this measurement as an index of cardiac function. Because it reflects left ventricular diastolic pressure, knowledge of PCWP is useful in judging cardiac performance, in guiding and assessing therapy, and in determining prognosis.[2] Measurement has traditionally required a hospital-based invasive procedure that has identified risks, patient discomfort, and considerable expense. A reliable noninvasive evaluation of PCWP is thus needed.

Radionuclide techniques have been used to assess both pulmonary blood flow patterns[3,4] and pulmonary blood volume (PBV).[5] Importantly, it has been shown that pulmonary blood flow is progressively redistributed toward the lung apex as left atrial pressure increases.[4] It has also been shown that PBV increases as left atrial pressure rises,[6,7] and that this increase may not be apportioned equally throughout the pulmonary vascular bed.[8,9] If PBV redistributes as left atrial pressure changes, a technique that measures the relative intravascular volume of lung apex and base should provide an index of PCWP. Technetium-99m equilibrium blood pool scintigraphy is a widely available, simple, low-risk, and rapid procedure that can assess relative distribution of intravascular volume. We therefore designed this study to determine whether knowledge of the relative distribution of technetium-99m labeled red blood cells in the lungs could be used to predict PCWP.

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Methods

Patients: Thirty patients (24 men, 6 women) participated in this study. All had undergone open-heart surgery (15 coronary artery bypass graft procedures; 7 mitral valvular replacements; 8 aortic valvular replacements) 2 days before the study, and had in place pulmonary artery balloon flotation catheters. The mean patient age was 63 ± 14 years (range 28 to 81). No patient had pulmonary artery systolic pressure >50 mm Hg, or known restrictive or obstructive lung disease. All patients were physically capable of sitting erect without support, and were undergoing wall motion scintigraphic studies for clinical reasons.

Protocol: PCWP was measured and recorded (Hewlett-Packard 7754A 4-channel strip recorder) during the performance of technetium-99m cardiac blood pool scintigraphy. Patients underwent nonzoomed imaging while sitting upright (24 patients), lying supine (19 patients), or in both positions (12 patients). Mean PCWP was measured at end-expiration during normal breathing. Zero calibration for determination of PCWP was at the mid-axillary line in the fourth intercostal space. After initial imaging, Albumisol® was administered at the rate of 250 ml/15 minutes if PCWP was <12 mm Hg, and repeated as necessary to increase PCWP to the clinically desired level. In 2 patients, elevated PCWP decreased during spontaneous diuresis in the early postinitial imaging time period. All patients who had changes in PCWP had concomitant imaging and PCWP determination repeated 60 to 120 minutes after initial imaging.

Imaging procedure: After intravenous injection of 30 mCi of technetium-99m in vitro labelled autologous red blood cells,[10] patients underwent imaging with a mobile scintillation camera (Ohio Nuclear 410) equipped with an all-purpose parallel-hole collimator and a mobile minicomputer (MDS Mugacart). Patients were imaged in 1 or more of 3 ways: posterior imaging while sitting erect (1 million counts, nongated); left anterior oblique (LAO) 45° gated imaging while sitting erect; LAO 45° gated imaging in the supine position. Gated images afforded 250,000 counts in each of 16 frames per cardiac cycle. Resulting images were displayed in a 64 × 64 word mode matrix.

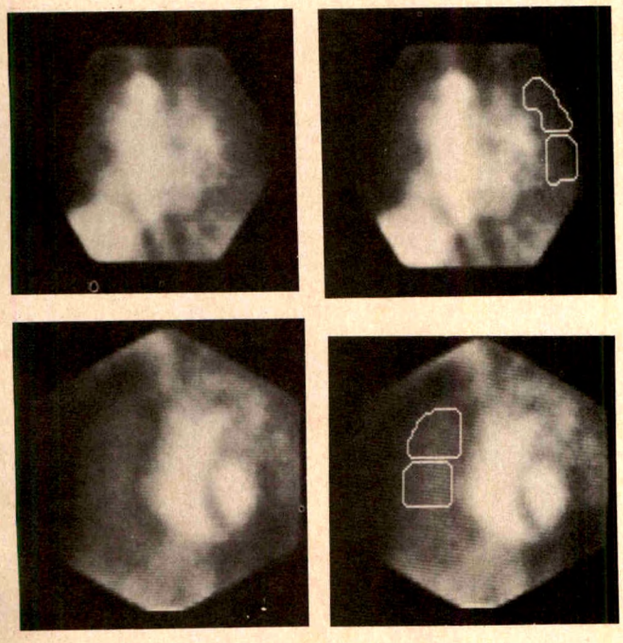

FIGURE 1. Posterior erect image (**top left**) with defined apical and basal regions of interest (**top right**). LAO 45° erect composite-gated image (**bottom left**) with apical and basal regions of interest (**bottom right**).

Image analysis: For analysis of the gated LAO views, images were added to form a composite static image, which then underwent 9-point smoothing. Analysis was done directly from the smoothed posterior view nongated images.

By manual light-pen manipulation, a variably shaped and sized region of interest (ROI) was defined over the right lung apex, and a second ROI was placed over the right lung base. The respective regions of interest were as large as possible (minimum 25 pixels), were placed so that cardiac and major vascular structures were avoided, and were placed well within the outer boundaries of the lung. The apical ROI extended as high as the level of the upper edge of the aortic arch, and the basal ROI extended to the mid-right ventricular level. The total area so delineated was divided in half, with the upper half being the apex and the lower half the base. Figure 1 displays the ROI selection for representative images of the posterior and LAO 45° positions.

After selection of appropriate regions of interest designated apex (A) and base (B), the average number of counts/pixel in each ROI was determined by computer. An apex/base count ratio was defined as the average number of counts per pixel in the apex divided by the average number of counts per pixel in the base.

Data analysis and statistical methods: The A/B radioactive count ratio was compared with the simultaneously obtained PCWP for (1) each of the 24 patients imaged in the posterior erect position; (2) each of the 14 patients imaged in the LAO erect position; and (3) each of the 19 patients imaged in the LAO supine position. A linear regression analysis by the method of least squares was performed to evaluate the continuous relationship between these 2 variables for each position. Further analysis (Friedman Anova test) was undertaken to determine the consistency of the A/B ratio in the 12 patients who had images performed in more than 1 position.

An A/B ratio that exceeded unity was defined as abnormal,[4] as was a PCWP >12 mm Hg.[6] To determine the sensitivity and specificity of an abnormal A/B ratio for an abnormal PCWP, chi-square analysis was used to compare A/B ratios stratified into those ≤1 or >1 with PCWP ≤12 or >12, within each imaging position. Sensitivity was defined as the proportion of patients with PCWP >12 mm Hg who also had an A/B ratio that exceeded unity. Specificity was defined as the proportion of patients with normal PCWP (≤12 mm Hg) who had a normal A/B ratio (≤1).

The ability of the A/B ratio to track changes in PCWP after intervention was analyzed for both directional change (Sign test) and magnitude of change (Wilcoxon test).

Results

Posterior erect position: Twenty-four patients were imaged in the posterior erect position. The A/B radioactive count ratios ranged from 0.71 to 1.30, with a mean ± standard deviation of 1.00 ± 0.20 (Table I). Concomitantly determined PCWP ranged from 5 to 26 mm Hg, with a mean value of 13 ± 6 mm Hg. When A/B ratio was plotted against PCWP (Fig. 2), a strong linear correlation was found (r = 0.864; p = 0.001), so that lower A/B ratios were seen with lower values of PCWP, and higher A/B ratios identified patients with higher wedge pressures. Stratification of A/B radioactive count ratios into normal (≤1) and abnormal (>1) values revealed that an abnormal A/B ratio was a sensitive and

TABLE I Comparison of A/B Ratios and PCWP for Each Imaging Position

	PCWP ≤12 mm Hg		PCWP >12 mm Hg		Overall	
	PCWP	A/B	PCWP	A/B	PCWP	A/B
Posterior erect						
M ± SD	9 ± 2	0.89 ± 0.12	18 ± 4	1.14 ± 0.08	13 ± 6	1.00 ± 0.20
Range	5–11	0.71–1.02	14–26	1.02–1.30	5–26	0.71–1.30
LAO 45° erect						
M ± SD	9 ± 2	0.94 ± 0.08	18 ± 4	1.19 ± 0.07	13 ± 6	1.10 ± 0.20
Range	6–12	0.85–1.08	14–25	1.10–1.27	6–25	0.85–1.27
LAO 45° supine						
M ± SD	9 ± 2	0.98 ± 0.11	17 ± 4	1.18 ± 0.13	13 ± 5	1.08 ± 0.20
Range	6–12	0.72–1.10	13–25	0.95–1.42	6–25	0.72–1.42

M ± SD = mean ± standard deviation.

TABLE II Comparison of the 3 Positions

	A/B-PCWP Correlation			Detection of Abnormal PCWP		
	r	n	p	Sens (%)	Spec (%)	Acc (%)
Posterior erect	0.86	24	0.001	100	83	92
LAO 45° erect	0.85	14	0.001	100	88	93
LAO 45° supine	0.69	19	0.001	90	67	79

The *r* value was determined by the method of least squares. Acc = accuracy (correct prediction of normal versus abnormal PCWP); n = number of patients; Sens = sensitivity; Spec = specificity.

specific indicator of an abnormal (>12 mm Hg) wedge pressure (Table II).

Of the 24 patients studied in the posterior erect position, 9 had control wedge pressures ≤12 mm Hg, and received an average of 500 ml of Albumisol each. Wedge pressure increased an average of 5 mm Hg (range 2 to 8). In 8 of 9 cases, A/B increased along with the increase in PCWP. In 1 patient, PCWP increased from 8 to 13 mm Hg and A/B did not change. In 2 patients, PCWP decreased after spontaneous diuresis; A/B decreased in both of these patients. These changes in A/B that accompanied changes in PCWP were significant in both direction (p = 0.04, Sign test) and magnitude (p = 0.01, Wilcoxon test).

For the posterior erect position, therefore, there was a strong correlation between PCWP and A/B, and a strong correlation between changing levels of PCWP and changing A/B. In addition, an A/B ratio greater than unity was strongly predictive of a PCWP >12 mm Hg.

LAO erect position: Fourteen patients were imaged in the LAO erect position. Mean PCWP was 13 ± 6 mm Hg (range 6 to 25), and mean A/B was 1.10 ± 0.20 (range 0.85 to 1.27) (Table I). The correlation between PCWP and A/B was also found to be strong in this position: $r = 0.842$, p = 0.001 (Fig. 3). Further, only 1 patient had a PCWP that was misclassified by the A/B ratio (Table II).

Four patients received volume with repeat imaging. In these patients, PCWP increased an average of 6 mm Hg, and A/B increased an average of 0.15. In all cases PCWP and A/B increased. Probably because of insufficient numbers of patients, the changes were not significant in direction (p = 0.13, Sign test) or magnitude (p = 0.07, Wilcoxon test).

LAO supine position: Nineteen patients were imaged in the LAO supine position. Mean PCWP was 13 ± 5 mm Hg, while mean A/B ratio was 1.08 ± 0.20

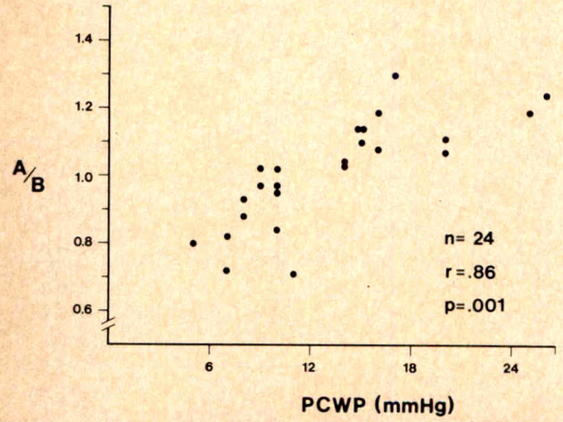

FIGURE 2. Values of A/B radioactive count ratio plotted against simultaneously measured PCWP in 24 patients imaged in the posterior erect position.

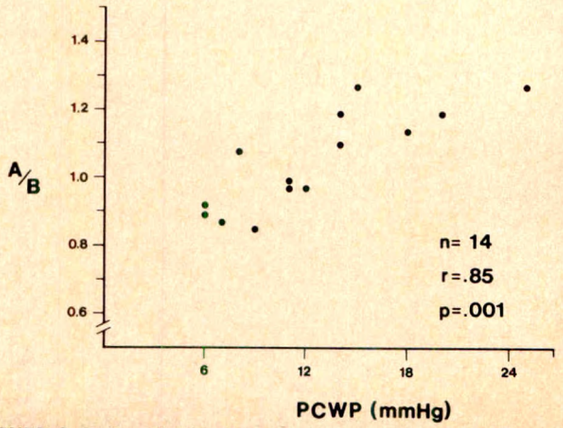

FIGURE 3. Ratios of A/B plotted against simultaneously measured PCWP in 14 patients imaged in the LAO 45° erect position.

(Table I). There was a positive correlation between PCWP and A/B, but it was not as strong as with erect imaging: $r = 0.678$, $p = 0.001$ (Fig. 4). Two of 12 patients with an A/B ratio >1.00 had a PCWP <12, and 2 of the 6 patients with A/B <1.00 had a PCWP >12 mm Hg. The sensitivity (90%), specificity (67%), and accuracy (79%) of an abnormal A/B ratio for an abnormal PCWP were considerably lower than for erect imaging (Table II). Eight patients received volume, and in all cases A/B increased along with the recorded increases in PCWP ($p = 0.01$, Sign test; $p = 0.01$, Wilcoxon test).

Correlation between the 3 positions: Twelve patients were imaged sequentially in the posterior erect, LAO 45° erect, and LAO 45° supine positions, with PCWP determined during imaging in each position. The A/B radioactive count ratios were compared for each position using the Friedman Anova test. Values obtained in the posterior erect position were found to be significantly less than those in the LAO 45° erect or supine positions ($p < 0.01$). Paired analysis with the Wilcoxon test revealed a significantly lower ($p = 0.03$) A/B ratio for posterior versus LAO 45° erect positions, and no significant difference between supine or erect LAO 45° values. When the ratios were compared across the 3 positions for the 11 male patients (Table III), the measurements in the posterior erect position were still significantly smaller than those in the LAO 45° positions. Female patients could not be examined without male patients because only 1 was imaged in all 3 positions.

Directional changes in A/B ran parallel to changes in PCWP in the posterior and supine positions. A direct numerical correlation between changes in A/B and changes in PCWP was not obtained for these positions ($r = 0.56$, $p = 0.07$; $r = 0.57$, $p = 0.14$, respectively).

Discussion

Pulmonary blood flow is normally distributed preferentially to the lung base, particularly in the upright position.[3] A redirection of blood flow toward the lung apex has been shown to occur as left ventricular filling pressure increases.[4,11] This reflects a greater relative distensibility of apical vessels, a constriction of basal vessels, and a recruitment of apical vessels that are usually closed.[12] However, blood flow is also highly dependent upon a number of factors that influence arteriolar resistance including posture, intraalveolar pressure, and adrenergic activity.[12] The distribution of pulmonary blood volume might be expected to be less sensitive to such changes, and thus to relate more directly to pulmonary venous (left ventricular filling) pressures. Indeed, pulmonary blood volume has been demonstrated by indicator dye techniques to progressively increase as left ventricular filling pressure increases, at least until exceedingly high pressures are reached.[13] The results of our study show that there is relatively more of total pulmonary blood volume in the lung base at low ventricular filling pressures, but that the apex-to-base distribution of PBV changes when PCWP rises.

TABLE III Comparison of A/B Ratio Obtained in 11 Male Patients Imaged Sequentially in 3 Positions

Position	A/B Ratio (Mean ± SD)	Range
Posterior erect	0.97 ± 0.16*	0.72–1.24
LAO 45° erect	1.01 ± 0.16	0.85–1.27
LAO 45° supine	1.08 ± 0.19	0.72–1.42

* $p < 0.01$, posterior erect versus LAO 45° erect or supine (Friedman Anova).
SD = standard deviation.

In this study, it was observed that when patients undergo imaging in the upright position, accurate estimates of wedge pressure can be made from the relative distribution of technetium-99m labeled red blood cells to the lung apex and base. In addition to providing a numerical estimate of PCWP, in the erect imaging positions this method clearly allows highly accurate identification of patients with abnormally elevated wedge pressures. Further, changes in A/B ratio track appropriately with directional changes in PCWP after intervention.

The correlation between A/B radioactive count ratios and PCWP was demonstrated to be less strong with supine imaging. This should not be surprising, as physiologic and previous radionuclide studies[4,12] have demonstrated a change in blood flow patterns with a change in posture. The reflexes that redirect blood distribution to the lung apex as wedge pressure increases remain intact,[12] but are blunted by the loss of similarly directed gravitational effects.

We attempted to establish which erect imaging position provided the best capability of evaluating PCWP. The posterior position obviates the problem of basal radioactive count attenuation due to increasing thickness as the anterior chest wall descends. This is the probable explanation for the lower A/B ratios at any given PCWP found in the posterior position. Because there was a strong correlation between A/B and PCWP for both erect positions, and because similar accuracies were found for detection of abnormal PCWP, it is dif-

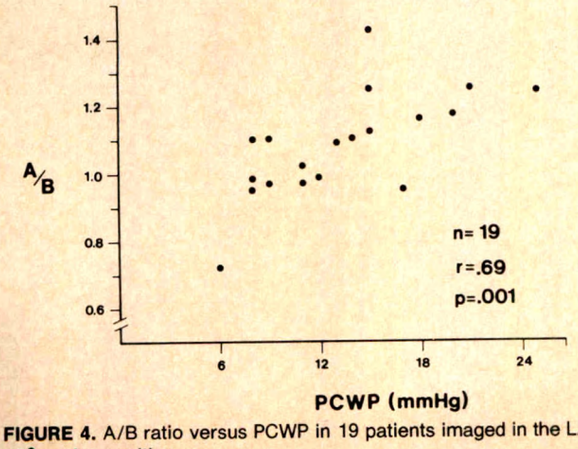

FIGURE 4. A/B ratio versus PCWP in 19 patients imaged in the LAO 45° supine position.

ficult on other than theoretical grounds to favor the posterior imaging position over the anterior.

Although this study has demonstrated the ability of an A/B ratio to estimate PCWP, the study population was too small for confident derivation of specific regression equations that might allow precise determination of PCWP. In addition, our patient group is not ideal for this purpose, because these early postoperative patients often have pleural effusions, atelectasis, and anatomic disruptions that may considerably affect the normal relationship between PCWP and A/B ratio. The finding of an imperfect relationship between changing levels of PCWP and changing A/B ratios probably also reflects this problem, as "leaky" vasculature is common early after open-heart surgery, excessive volume was frequently required to make small changes in PCWP, and an increased extravascular lung fluid would lead to intravascular radioactive count attenuation and changed A/B-PCWP relationships. Other limitations exist for the precise determination of PCWP by equilibrium blood pool scintigraphy: (1) The A/B ratio will be affected by the relative amounts of radioactivity arising from or attenuated by non-PBV sources. In thick-chested or big-breasted patients, considerable relative attenuation of counts from the lung base might be expected. (2) Although a linear correlation was observed within the range of wedge pressures studied (5 to 26 mm Hg), there will be a limit to the increased distribution of PBV to the lung apex, with further increases in PCWP leading to fluid extravasation rather than to increased PBV or to changes in the distribution of PBV. (3) The radioactive counts are accumulated over time, involving therefore potential inaccuracies due to patient movement during imaging. In addition, if the basal ROI is placed too low, the possibility exists that subdiaphragmatic counts may be sampled during expiration.

Assessment of pulmonary blood volume using radionuclide techniques has previously been reported. Nichols et al[8] used inhaled carbon-14–labeled carbon monoxide and positron blood-pool imaging to detect the development of left ventricular dysfunction in exercising patients: pulmonary blood volume increased only in those patients developing exercise-induced ischemia. Okada et al,[7,14] using technetium-99m, then showed that a ratio of counts, postexercise to preexercise, within a single ROI, allowed improved detection of patients with significant coronary artery disease[14] and reflected changes in PCWP during exercise.[7] Urbina et al[9] first demonstrated the potential usefulness of an apex-to-base ratio of PBV distribution in differentiating normal from abnormal PCWP. In their study however, they found a relatively poor correlation between A/B and PCWP, probably because imaging was supine, technetium labelling was in vivo, the selected regions of interest were small, and as much as 2 weeks separated scintigraphic imaging and invasive PCWP measurements. Our study, by employing in vitro labelling and simultaneous scintigraphic-PCWP testing, establishes the existence of a correlation between A/B ratios and PCWP, extends its clinical applicability to patients imaged upright or supine, posteriorly or from the LAO 45° position, and demonstrates that changing A/B ratios track appropriately with changes in PCWP.

Other noninvasive techniques have been used to assess left ventricular filling pressure.[4,15] The method described herein is rapid, simple, and widely available, and can easily be incorporated into the routine radionuclide assessment of ventricular performance. It is potentially important that the red blood cells be labeled in vitro with technetium-99m.[10] This technique has been shown to result in a labelling efficiency of approximately 95% at 30 minutes after injection,[16] ensuring that the site of origin of radionuclear activity is nearly completely intravascular. As such, regional variation in counts over the lung fields will reflect regional variation in intravascular blood volume.

We believe that the PCWP-A/B correlation is a significant finding, in that PCWP can be approximated from routinely performed blood pool scintigrams. Moreover, observation of impact of therapeutic intervention on A/B ratios allows conclusions to be drawn about the effect that the intervention has had on PCWP. In centers that perform supine imaging, a less precise estimation of PCWP can be made in this position, or an additional upright view can easily be incorporated.

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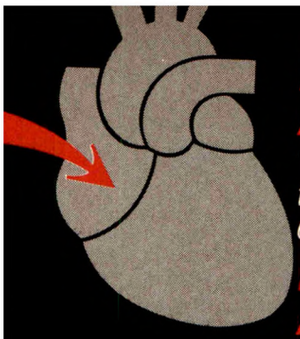

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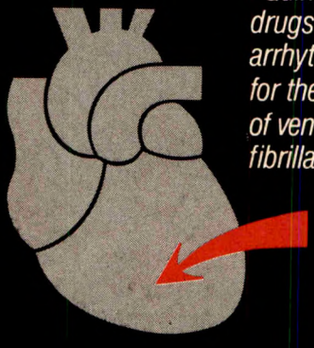

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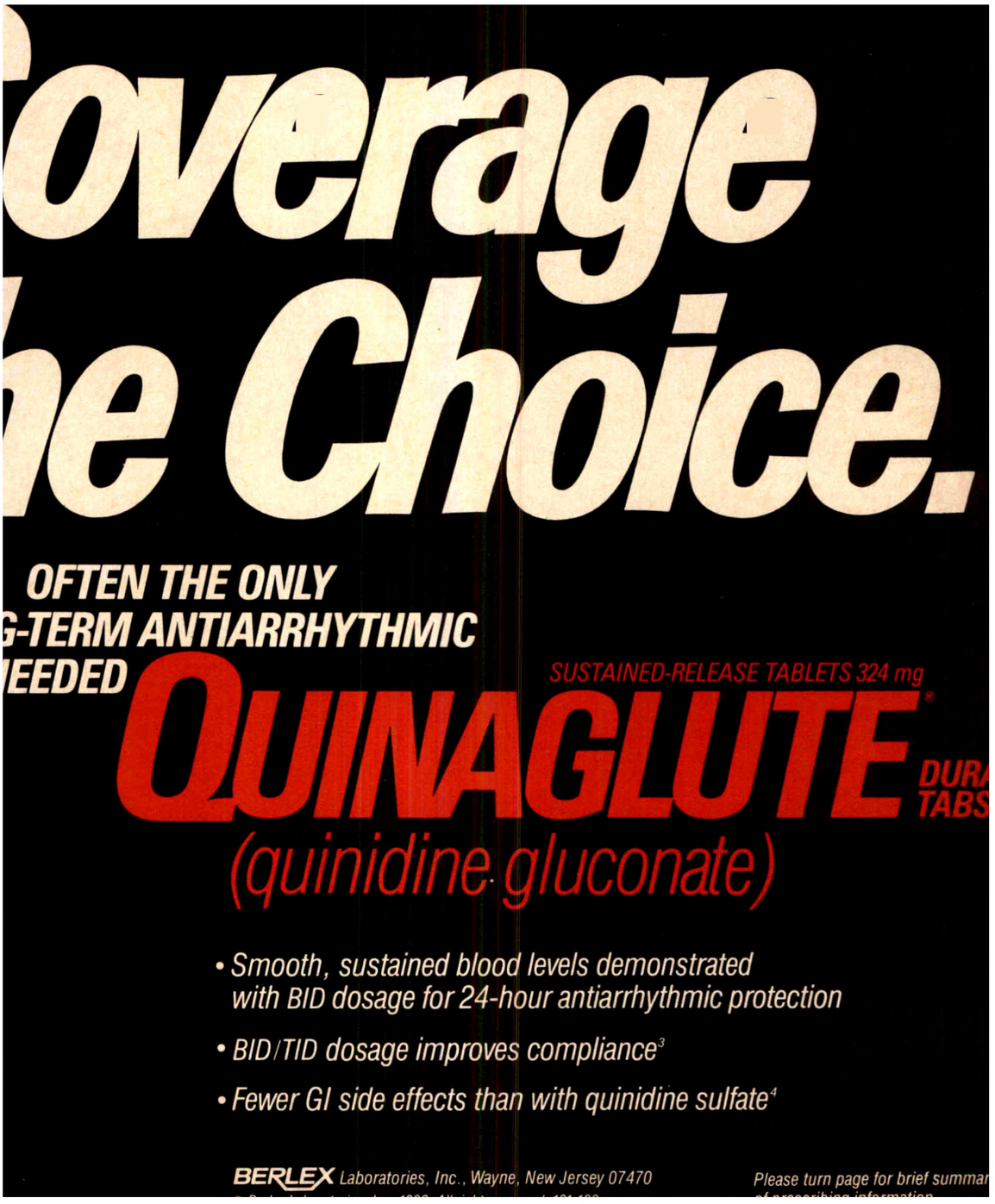
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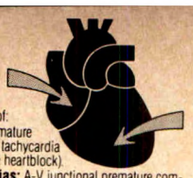

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CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
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Drug Interactions: *Drug*	*Effect*
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Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
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Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
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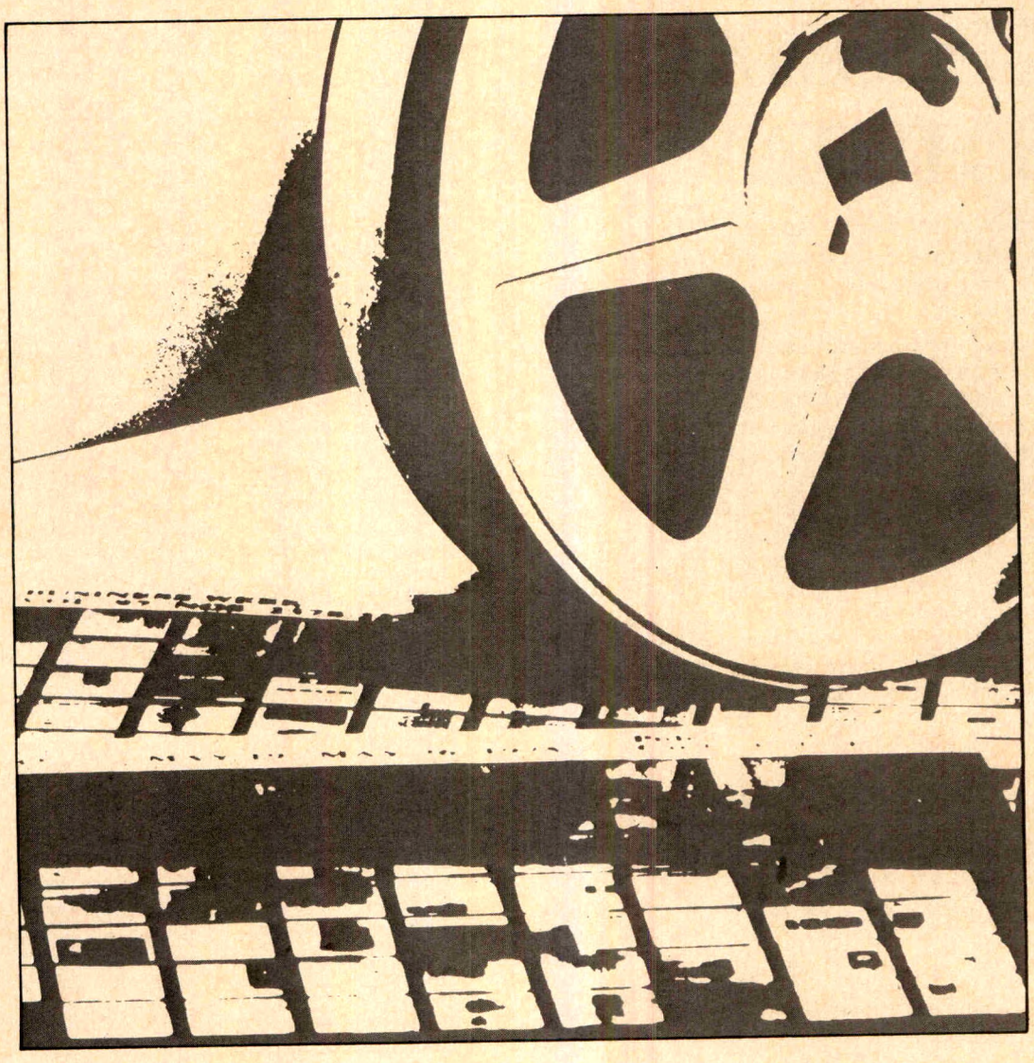

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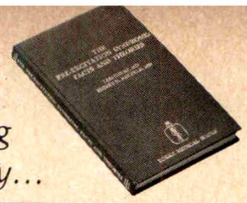

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC
Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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Your Right to Know... The Facts in Black and White

FACT: Calan® (verapamil HCl) is the calcium antagonist consistently demonstrating antianginal benefits equal to, or greater than, propranolol, at clinically used doses in angina of effort.[1,2,3,4,5,6]

- Calan is also effective in variant angina[7] (where spasm may be exacerbated by propranolol[8]) as well as in unstable angina.[9]

FACT: In direct-comparative studies, the antianginal benefits of Calan were reported to be unsurpassed by nifedipine.[10,11,12]

- In stable effort angina: "The trial demonstrated a clear difference in the antianginal efficacy of [verapamil (Calan) and nifedipine]. ...Verapamil [Calan] was more effective..."[10] In another study, the efficacy differences were not statistically significant.[11] The doses used in both studies were Calan 120 mg tid and nifedipine 20 mg tid.

  In variant angina, in the one published comparative study, Calan and nifedipine showed equal efficacy. However, this study was neither blinded nor randomized.[12]

- Studies were directly comparative, and responses to each drug were measured objectively.[10,11,12]

FACT: Calan is indicated as single-agent initial therapy for all types of angina, while nifedipine is not.[13,14]

- Nifedipine is indicated in stable effort angina only in patients refractory to or intolerant of nitrates and/or beta-blockers.[14]
- Nifedipine is indicated for unstable angina only when ECG findings indicate vasospasm or the disease is refractory to nitrates and/or beta-blockers.[14]

FACT: The potential serious cardiovascular side effects of Calan are similar to those of beta-blockers.

- Calan and propranolol have basically the same cardiovascular cautions and contraindications such as in patients with ventricular dysfunction, second- or third-degree AV block, or cardiogenic shock.[13,15] Calan is also contraindicated in the presence of sick sinus syndrome or hypotension.
- Calan rarely causes extreme fatigue or mental depression.
- Impotence, memory loss, or nightmares have not been associated with Calan use. Calan may cause constipation.
- Calan can be used without special caution in patients with angina who also have asthma, chronic obstructive pulmonary disease, diabetes mellitus, or peripheral vascular disease such as Raynaud's phenomenon.

FACT: The incidence of adverse effects of Calan and nifedipine merits comparison (see chart below).

Adverse Reactions Reported	nifedipine Uncontrolled U.S. experience in 2,100 patients. The incidence of adverse reactions in controlled studies was generally the same or higher.[14]	(Calan) verapamil Clinical studies in 1,166 patients — NOTE that similar results were seen in both controlled clinical trials and uncontrolled clinical experience.[13]
Dizziness, light-headedness	About 10%	3.6%
Constipation	2% or less	6.3%
Flushing	About 10%	*
Headache	About 10%	1.8%
Weakness	About 10%	*
Fatigue	*	1.1%
Nausea	About 10%	1.6%
CHF or pulmonary edema	**	0.9%
Peripheral edema	About 10%	1.7%
AV block: third-degree	*	0.8%
Transient hypotension	About 5%	2.9%
Palpitation	About 2%	*
Bradycardia: HR<50/min	*	1.1%
Syncope	About 0.5%	<0.5%

*Not reported in the prescribing information.[13,14]

**About 2%, "not readily distinguishable from the natural history of the disease." "It remains possible, however, that some or many of these events were drug related."[14]

Calan® (verapamil HCl) **TABLETS** 80 mg and 120 mg

Effective Angina Therapy

Please see reverse side for a brief summary of the complete prescribing information.

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The Facts of Effective Angina Therapy

FACT: Calan® (verapamil HCl) has pharmacologic effects complementary to those of nitrates.[13]

- Like propranolol, Calan decreases myocardial contractility. Calan's effect on the SA node tends to minimize heart rate response to arterial vasodilation, leaving the rate unchanged or slightly reduced.[13]
- Nifedipine tends to cause slightly increased heart rate due to a sympathetic response to arterial dilation.[14]

FACT: Calan provides truly additive effects with propranolol when such combination therapy is necessary in the treatment of chronic stable angina.[3,4]

- In two studies involving a total of 33 patients, the additive effects of Calan with propranolol on exercise tolerance could be seen.

	Study A[3]	Study B[4]
Propranolol alone	+2 min *	+1.3 min
Calan alone	+3.2 min	+3.4 min
Calan with propranolol	+5.3 min	+4.7 min

*Difference from placebo to maximally tolerated exercise

- Combined therapy should be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Because of the still limited experience with combination therapy, Calan should be used alone, if possible.

FACT: Safety considerations are important with Calan, beta-blockers, and nifedipine.

- In patients with normal conduction, Calan's electrophysiologic effects are rarely clinically important.[13] However, Calan's contraindications include patients with sick sinus syndrome or second- or third-degree AV block.
- The concomitant use of digitalis with Calan or nifedipine requires caution because digoxin serum levels may increase.[16,17]
- Both Calan and nifedipine, as well as propranolol and nitrates, require monitoring during upward dose titration.[13,14,15]

For Your Patients With Angina...

Calan® TABLETS 80 mg and 120 mg
(verapamil HCl)

- Calan is the calcium antagonist with consistently demonstrated antianginal benefits equal to or greater than propranolol.
- Calan is effective in variant angina where spasm may be exacerbated by propranolol.[8]
- Calan, unlike nifedipine, has a first-line indication for stable effort angina.

FACT: All the above statements are supported by published materials.

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Calan® (verapamil HCl) TABLETS 80 mg and 120 mg

Contraindications: Severe left ventricular dysfunction (see *Warnings),* hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Occasional elevations of liver enzymes have been reported; patients receiving verapamil should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil. **Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefuly monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR< 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** Calan (verapamil HCl) is supplied in 80-mg and 120-mg sugar-coated tablets.

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Sustained Limitation of Myocardial Necrosis 24 Hours After Coronary Artery Occlusion: Verapamil Infusion in Dogs With Small Myocardial Infarcts

DEREK M. YELLON, PhD, DAVID J. HEARSE, DSc, MILES P. MAXWELL, BSc, DAVID E. CHAMBERS, BS, and JAMES M. DOWNEY, PhD

Studies were undertaken to ascertain whether verapamil infusion affords a sustained limitation of myocardial injury in the dog after a 24-hour period of coronary artery occlusion. Regional myocardial ischemia was induced by an embolization procedure which did not involve thoracotomy. Immediately after embolization radioactive microspheres were administered intraventricularly to define any area of myocardial underperfusion (zone at risk of infarction). Verapamil (0.005 mg/kg/min) was then administered and maintained for 24 hours during which time the dogs were allowed to recover from anesthesia. The control group received a corresponding infusion of saline solution. After 24 hours the dogs were killed and transverse myocardial sections (3 mm) were prepared. The resulting area of necrosis was visualized by tetrazolium staining, and risk zones were visualized by autoradiography. In the control heart, 62 ± 7% of the zone at risk deteriorated to necrotic tissue, whereas in the verapamil-treated group only 18 ± 4% of the tissue in the zone at risk became necrotic. *Verapamil appeared to exert a significant ($p < 0.001$) tissue-sparing effect that was sustained for at least 24 hours after the onset of ischemia.*

During the past decade, drugs have been proposed that were thought to protect the ischemic myocardium.[1,2] Unfortunately, due to methodologic limitations, none proved efficacious to the satisfaction of all.[3,4] In fact, even the concept of myocardial infarct (MI) size reduction itself remains the subject of debate.[1,3] One factor contributing to this controversy is the failure of past studies to differentiate between a delay and a sustained prevention of myocardial damage. Recent studies from this laboratory[4] indicate that at least 1 drug, flurbiprofen, produced sizable reductions in apparent MI size when evaluated 6 hours after coronary occlusion, but the protection disappeared on evaluation at 24 hours. One group of drugs proposed to protect the ischemic myocardium are the slow calcium-channel blocking agents. These drugs have been claimed to reduce tissue injury under experimental conditions,[5–9] but again, rarely has the distinction between delaying and reducing injury been made. In a recent study, De Boer et al[10] reported that verapamil reduced MI size approximately 20%. However, those hearts were examined only 8 hours after coronary artery occlusion. In this study we subjected dogs to 24 hours of coronary occlusion to determine whether verapamil can offer a long-term protective effect.

From the Myocardial Metabolism Research Laboratories, The Rayne Institute, St. Thomas' Hospital, London SE1, United Kingdom. This study was supported by grants from the British Heart Foundation and the Medical Research Council of Great Britain, and by Grant HL20648 from the National Heart, Lung, and Blood Institute, U.S. Public Health Service, Bethesda, Maryland.

Address for reprints: Derek M. Yellon, PhD, Myocardial Metabolism Research Laboratories, The Rayne Institute, St. Thomas' Hospital, London SE1, U.K.

Methods

Surgical procedures: Twenty-five greyhounds of both sexes ranging from 20 to 32 kg were anesthetized with pentobarbital sodium (30 mg/kg intravenously). Each dog also received 500,000 units of penicillin intramuscularly at the time of anesthetization to prevent infection during the subsequent experimental period. The animals were intubated and the respiration was controlled with a mixture of nitrous oxide and air. After anesthesia, a catheter was placed in the femoral artery for subsequent withdrawal of a reference sample of blood during radioactive microsphere infusion. The left carotid artery was exposed through a midline cervical incision and a specially made cannula[11] (attached to a pressure transducer) was inserted into the carotid artery and advanced down to the aortic root. The cannula was then advanced into the coronary ostium by manual probing, precise placement of the cannula being confirmed by a transition in the recorded

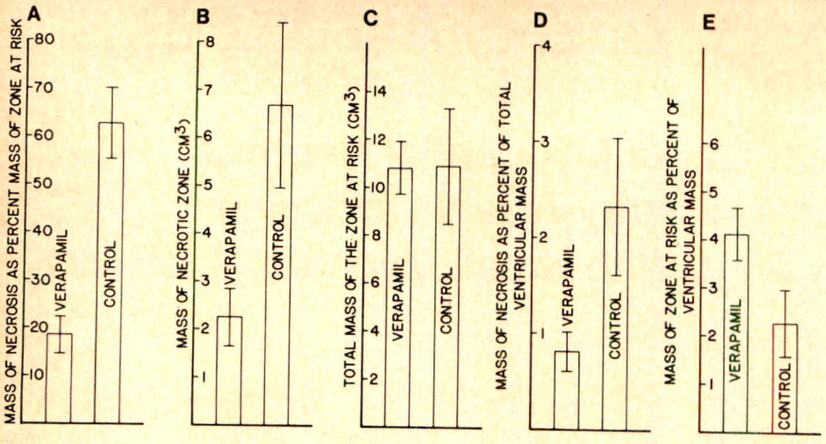

FIGURE 1. Effect of verapamil infusion or saline infusion on (**A**) the mass of necrosis (as defined by tetrazolium staining) expressed as a percentage of the zone at risk (as defined by microsphere autoradiography); (**B**) the total mass of necrotic tissue; (**C**) the total mass of the zone at risk; (**D**) the mass of necrosis expressed as a percent of the total ventricular mass; (**E**) the mass of the zone at risk expressed as a percent of the total ventricular mass. Each value is the mean of 8 hearts; **bars** represent standard error of the mean.

pressure from an aortic value of approximately 175 mm Hg to a peripheral coronary pressure of approximately 20 mm Hg. After placement of the cannula in the coronary ostium, a plastic bead, 2.5 mm in diameter, suspended in 20 ml of saline solution was injected through the cannula to cause coronary embolization. The cannula was then withdrawn from the coronary ostium and advanced past the aortic valve into the left ventricle (again pressure tracing confirms correct placement of the cannula in the ventricle). Cerium-141–labeled microspheres (20 million), 15 μm in diameter, were then injected through the cannula into the left ventricle. Immediately before microsphere administration, a 90-second withdrawal of arterial blood from the femoral artery was initiated. This blood sample served as a reference standard for calculation of regional myocardial blood flow.[12] After microsphere injection, the cannula was removed and the dogs were randomly divided into treatment or control groups.

Verapamil (Abbott Laboratories, United Kingdom) was prepared in normal saline solution, 0.2 mg/ml. The animals in the treatment group received a bolus injection of verapamil (0.2 mg/kg intravenously) over 2 minutes followed by a constant infusion of the drug in saline solution using an automatic pump set to deliver 0.005 mg/kg min^{-1} for up to 24 hours. The control dogs received a constant infusion of saline solution over 24 hours. Drug or saline infusion was initiated within 5 minutes of coronary embolization in all animals. Carotid exposure was then reconstructed and the animals were returned to the recovery room. To prevent thrombus formation behind the emboli, heparin (5,000 units) was added to the infusion solution in both drug and control groups. Blood samples in the treatment group were obtained periodically to determine serum drug levels. All operations were performed under strict sterile conditions to minimize the risk of infection. Heart rate, electrocardiogram, and blood pressure were recorded continuously during the operative procedure. Blood pressure changes after the bolus injection of verapamil were monitored to ensure that it did not decrease by more than 25 mm Hg.[5]

Subdivision of animals: A total of 25 dogs were used in this study. Six were excluded as a consequence of aortic rupture or aneurysm (from manual probing with the cannula) during the early operative phase. An additional 3 dogs (1 control and 2 drug-treated) were excluded as they died within 8 hours of coronary embolization, presumably as a result of ventricular fibrillation. Of the remaining 16 dogs, 8 were randomly assigned into the drug treatment series and 8 into the control group.

Tissue preparation: At the end of the 24-hour period, animals were reanesthetized and the chest was opened. The heart was removed and rinsed in water; 200 ml of isotonic saline solution at 23°C was then infused into the vasculature through the root of the aorta. The heart was then weighed and the location of the bead in the coronary bed noted. All beads were lodged either in branches of the left anterior descending coronary artery or in the circumflex artery. The heart was then frozen and sliced transversely into 3 mm thick sections using an electric meat slicer.

Histochemical visualization of zones of necrosis: To identify tissue that had become necrotic, tissue slices were immersed in a mixture of 0.4% weight/volume triphenyl tetrazolium and 0.04% weight/volume nitro blue tetrazolium in phosphate buffer (0.07 *M*, pH 7.4) at 37°C and then incubated for 20 minutes.[13,14] Viable tissue stains violet whereas necrotic tissue remains pale. The slices were then blotted dry and necrotic areas painted with a fluorescein dye to enhance interface definition.

Autoradiographic visualization of risk zones: After tetrazolium staining, the tissue slices were placed on an acrylic sheet (20 by 25 by 0.4 cm). A layer of plastic film was placed over the tissue slices, followed by a second acrylic sheet. The 2 acrylic sheets containing the stained tissue were then placed in a clamping device and frozen. Once frozen, a sheet of X-ray film (Kodak no screen NS-2T) was interposed between 1 acrylic sheet and the tissue slices, and the whole assembly was placed in a lightproof box at −20°C for a 24-hour exposure period. Just before this step, the exact position and orientation of each tissue section on the film were marked by passing a sharpened metal probe through 2 predrilled holes in the acrylic sheets, piercing both the film and the tissue. After the 24-hour exposure period, the film was removed and developed using standard developing processing methods.

Data analysis: After removal of the x-ray film for developing, the tissue slices (still frozen to 1 acrylic sheet) were taken to a cold room where a sheet of clear acetate was placed over the slices. The outline of the tissue, the 2 register holes, and the infarct were traced. The acetate sheet was then overlaid on the X-ray film using the 2 register holes to ensure precise alignment. The X-ray film revealed the blood flow pattern around the area served by the occluded artery and thus delineated the risk zone. The superimposition of the acetate tracing of the zone of necrosis on the autoradiogram thus allowed the detection of any tissue salvage or infarct extension relative to the original zone at risk. The volume of the region at risk was calculated by computerized planimetry of the risk zone for each slice and multiplying this figure by its thickness (3.0 mm). The values for the sequential slices were then added to provide the total volume for each heart.

Using the same procedure, the total volume of necrotic tissue was calculated. All results are expressed in terms of mean ± standard error of the mean (SEM).

Regional blood flow measurements: To quantitate regional myocardial blood flow, 4 samples (approximately 250 mg each) were taken from selected sites of each heart. With tetrazolium staining as a guide, 2 samples were taken from the center of the necrotic region, 1 epicardial and 1 endocardial, and 2 samples were taken from the well perfused myocardium, again epicardial and endocardial. The tissue samples were weighed and their radioactive content was measured. Blood flow was calculated using the standard equation.[15] Ischemic blood flow was expressed as a percentage of that obtained from samples taken from the well perfused myocardium and results were expressed in terms of mean ± SEM.

Results

Control series: Figure 1 (panel A) reveals that 62 ± 7% of the volume of tissue in the zone at risk, as defined by autoradiography, had become necrotic 24 hours after coronary artery occlusion. The mean volume of necrotic tissue was 6.6 ± 1.7 cm^3 (panel B), whereas the mean volume of the zone at risk (panel C) was 10.8 ± 2.4 cm^3. Thus, even in the absence of any therapeutic intervention (other than saline infusion), a proportion of the zone at risk was spontaneously "salvaged." Although not specifically investigated in this study, the greatest proportion of sparing appeared to be in the epicardial zone.

Verapamil-treated series: Figure 1 (panel A) shows that verapamil infusion dramatically reduced the volume of necrotic tissue. The volume of necrosis expressed as a percent of the zone at risk was only 18 ± 4%, which was significantly ($p < 0.001$) lower than that in the control group. Figure 1 (panel B) also shows that the absolute volume of necrotic tissue was significantly ($p < 0.05$) lower in the verapamil-treated group. A similar trend is obtained when the results are expressed as a percent of the total ventricular mass (panel D). However, there was no statistical difference between the control and verapamil-treated groups when expressed in this way. In comparing the verapamil-treated and control groups (panel C), no significant difference ($p < 0.10$) was noted between the total volume of the zones at risk.

Figure 2 shows the relation between the volume of the initial zone at risk (expressed as a percent of the left ventricular volume) and the volume of the final zone of necrosis (again expressed as a percent of left ventricular volume) after 24 hours of ischemia in both control and verapamil-treated groups. Individual points separate into 2 clearly defined populations, confirming that the drug-treated heart had a smaller volume of necrotic tissue and that in both groups the final volume of necrosis is directly proportional to the initial volume of tissue at risk.

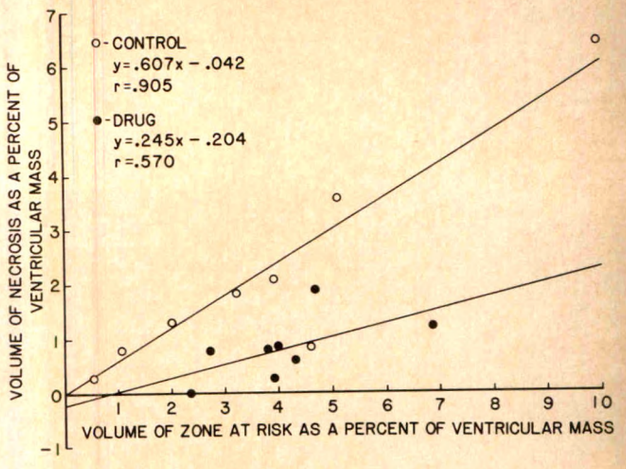

FIGURE 2. Correlation between the mass of necrotic tissue as measured at the end of 24 hours of ischemia (expressed as a percentage of ventricular mass) and the mass of the zone at risk as found at the onset of ischemia (expressed as a percentage of ventricular mass).

Hemodynamic observations: In a preliminary attempt to investigate the mechanisms underlying the verapamil-induced protection, a number of hemodynamic measurements were made before and after coronary embolization in both control and verapamil-treated dogs.

Measurements of systolic, diastolic, and mean blood pressure together with heart rate can be seen in Table I. Before embolization, there was no significant difference in any hemodynamic index between the 2 groups. Measurements taken within 5 minutes of embolization revealed that coronary occlusion had no immediate effect on any index of function. Furthermore, there was no significant difference between control dogs and those about to receive verapamil infusion. After verapamil

TABLE I Hemodynamic Assessments Before and After Coronary Artery Embolization

	Control Group				Verapamil-Treated Group			
	Blood Pressure			Heart Rate (beats/min)	Blood Pressure			Heart Rate (beats/min)
	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)		Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)	
Preembolization	220 ±7	165 ±5	193 ±6	160 ±6	207 ±11	164 ±5	186 ±8	153 ±9
Postembolization	211 ±7	161 ±5	186 ±6	166 ±6	216 ±8	157 ±5	186 ±4	152 ±10
Drug infusion	211 ±7	161 ±5	186 ±6	166 ±6	191 ±11	132 ±11	162 ±11	140 ±11

TABLE II Residual Blood Flow During Regional Myocardial Ischemia

Group	Residual Blood Flow in Ischemic Tissue*	
	Epicardial Tissue	Endocardial Tissue
Control group before saline infusion	20 ± 6%	9 ± 3%
Drug group before verapamil infusion	14 ± 5%	8 ± 5%

* Expressed as a percentage of that in remote nonischemic tissue.

infusion, a significant and sustained reduction occurred in both systolic and diastolic pressure such that within the verapamil-treated group there was an average decrease of 24 mm Hg in mean arterial pressure. Saline infusion in the control group caused no significant hemodynamic change.

Regional blood flow measurements: To ascertain some indication of the level of collateral flow supplying the tissue after occlusion, microsphere radioactivity measurements were made. The results (Table II) indicate that in the control group of hearts, flow in the ischemic zone was reduced 80 to 90%; the mean value for collateral flow in the endocardial samples was 9.1 ± 2.8% of that measured in the nonischemic tissue remote from the ischemic zone. In the epicardial tissue, flow was somewhat higher at 20.1 ± 5.6%, reflecting the previously described[16,17] transmural gradient for residual flow. In the verapamil group, as expected, the results were the same because the microspheres were administered before the initiation of verapamil infusion.

Discussion

These results indicate that verapamil exerts a marked protective effect against ischemia in the dog heart. This protection was afforded to smaller infarcts than most other investigators employ. Part of our choice of small regions of ischemia is relative to contraints of the cannula we use to embolize the coronary vessels. A 2.5 mm diameter bead is as large as the cannula will accommodate. Another reason for our choice is to optimize the sensitivity of the method. Because the collateral support to an ischemic region is inversely related to its size,[18] drug-induced salvage is more likely to occur in a small infarct than in a large one.[19] Furthermore, the infarcting hearts are uncomplicated by cardiac decompensation and arrhythmias should be less of a problem.

We observed 38% spontaneous salvage in the control group. The reported amount of spontaneous salvage that occurs in an untreated dog varies widely in the literature. In previous studies with this same model we observed only about 10% spontaneous salvage.[4,20] Several possible explanations exist for the higher values in the present study. One control dog had only 18% necrosis of the risk zone. We have no explanation of why that occurred because the collateral flow, as revealed by the microspheres, was not abnormally high. Therefore, we included that dog in the data set. However, without that animal, the mean salvage would have been 31% which is still higher than our previous experience. There may be seasonal influences as the 2 studies were performed at different times of the year. Studies that use stereoangiography to delineate the risk zone routinely report a much higher percent of spontaneous salvage[21,22] as compared with those using dyes[23,24] or autoradiography.[4,10,24] Apparently, the stereoangiography technique systematically overestimates the risk zone and those values of spontaneous salvage are thus artifactually high.

Studies using the stereoangiography technique indicate that infarction will not occur when the risk zone involves 20% or less of the ventricle. Our results would not agree with that conclusion as the risk zones in the control group only involved 2.3% of the ventricular mass and still showed sizable infarcts. That earlier conclusion was probably a product of the systematic overestimation artifact of the risk zone by the stereoangiographic method.

A critical factor contributing to the confusion and misinterpretation of protection studies is the failure to distinguish between *reducing* and *delaying* injury. As we illustrated with the anti-inflammatory agent flurbiprofen[4] (which substantially delayed but did not ultimately reduce injury), assessments of injury as soon as 6 hours after the onset of ischemia are too soon to distinguish between delaying and preventing injury. For this reason we chose 24 hours elapsed ischemia in these studies with verapamil, and in contrast with our flurbiprofen studies we were able to show a sustained reduction of injury. Tissue that survives at the 24-hour time period is most likely to be in a stable state and unlikely to subsequently necrose. Whether survival would have continued if verapamil had been withdrawn at the 24-hour mark was not examined and must be the subject of future studies.

The possibility that verapamil may reduce the severity of myocardial ischemic injury after experimental occlusion was suggested as early as 1968 by Sodi-Pallares et al.[25] They reported that the drug was able to prevent or reverse electrocardiographic indexes of myocardial ischemia in the dog. Since then there have been relatively few studies on the effect of verapamil on infarct size in large animals. Smith et al[6–8] showed that in the dog heart with coronary artery occlusion, verapamil reduced S-T segment elevation. However, no effects on metabolism, blood flow, or enzyme levels could be detected in the ischemic tissue as a consequence of treatment.[7] Reimer et al[5] first demonstrated that verapamil could reduce necrosis during myocardial infarction. In their study the drug was given before as well as after infusion, and a very short duration of ischemia was employed (40 minutes) followed by a lengthy reperfusion (2 to 4 days). De Boer et al[10] found that verapamil reduced infarct size by a modest 20% when dogs were examined 8 hours after occlusion. To date, the only suggestion of a sustained effect of verapamil in permanent occlusion is the 1979 abstract by Ribeiro et al[26] in which they reported a 50% reduction in necrosis. Our study supports their claim.

Certain characteristics indicate that calcium antagonists are not totally homogeneous. Verapamil, D600,

and diltiazem have an almost equal calcium antagonistic effect on myocardium, pacemakers, and the vasculature, whereas nifedipine and its derivatives are prominent vasodilators and suppress contractility. However, their influence on cardiac pacemakers is small.[27] In the latest work by Zalewski et al[28] in which 5 calcium antagonists were tested, the investigators showed that *despite differences* in hemodynamic and electrophysiologic properties, all calcium antagonists tested reduced mortality and equally protected the ischemic myocardium 6 hours after coronary artery occlusion in the dog heart. Thus, the mechanism whereby verapamil limited the extent of necrosis in our study is not clear at present but might include (1) blocking ischemia-induced intracellular calcium overload and its consequent problems; (2) reducing the energy demand-supply ratio through the negative inotropic effects of the drug; or (3) specifically enhancing coronary flow to the ischemic zone. Clarification of these and other possibilities is the subject of our current investigations.

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Diastolic Synchronized Retroperfusion Versus Reperfusion: Effects on Regional Left Ventricular Function and Myocardial Blood Flow During Acute Coronary Occlusion in Dogs

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The effects of 170 minutes of diastolic synchronized retroperfusion of the coronary sinus with arterial blood during 180 minutes of coronary artery occlusion on regional myocardial contractility (ultrasonic crystals) and blood flow (microspheres) were investigated in open-chest dogs. These effects were compared with those of 180 minutes of coronary occlusion and those of 170 minutes of anterograde reperfusion after 10 minutes of coronary occlusion in separate groups of dogs. Retroperfusion was able to almost restore transmural blood flow in the moderately ischemic zones and to increase it back to 47% of its preocclusion value in the severely ischemic zones with, in both zones, a favorable redistribution of flow toward the endocardium. Simultaneously, retroperfusion significantly improved segment length shortening in the moderately ischemic zones and significantly reduced the extent of paradoxical bulging in the severely ischemic zones. These partial recoveries in regional contractility and blood flow during retroperfusion were intermediate between those induced by 170 minutes of anterograde reperfusion and those of 180 minutes of coronary artery occlusion. Thus, in the presence of coronary artery occlusion, retroperfusion appears to exert a beneficial effect by improving both regional perfusion and function in the ischemic zones and may be proposed as a medical circulatory support to the jeopardized myocardium.

Coronary sinus retroperfusion with arterial blood was proposed as a possible method for treating myocardial ischemia as early as 1898.[1] Initial approaches, such as the Beck procedures,[2] were surgically oriented and consisted of anastomosing a venous graft between the aorta and the coronary veins in patients with chronic and diffuse coronary artery disease. Despite short-term clinical improvement, this technique was discarded since longer follow-up pathologic studies revealed significant damage to the coronary venous system and severe venous congestion. Subsequent retroperfusion techniques were medically oriented. Meerbaum et al[3] reported a pulsatile coronary venous retroperfusion system, synchronized with the cardiac cycle, and Farcot et al[4,5] developed a balloon-tip catheter which selectively delivers arterial blood through the great cardiac veins in diastole and allows coronary venous drainage in systole. Experimental studies by these groups have shown that diastolic synchronized retroperfusion improved myocardial metabolism and contractility and reduced the size of the ischemic zone without obvious coronary venous damage after several hours of retroperfusion.[4] More recently, Berdeaux et al[6] demonstrated with the radioactive microsphere technique that diastolic synchronized retroperfusion was capable of restoring nutritional blood flow to the ischemic myocardium up to approximately 50% of normal control flow with a preferential redistribution of flow toward the endocardium of the ischemic zone. However, the relationship between changes in regional myocardial blood flow and changes in segmental function during retroperfusion has not yet been examined.

Thus, the goal of the present investigation was to determine whether or not the increase in regional myocardial blood flow induced by diastolic synchronized retroperfusion during permanent coronary occlusion is associated with contractile function recovery

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of the ischemic myocardium. The effects of retroperfusion during a 3-hour coronary occlusion period were compared with those observed in a control occlusion group and in an anterograde reperfusion group.

Methods

Twenty-two adult mongrel dogs of both sexes, weighing 22 to 34 kg, were anesthetized intravenously with sodium pentobarbital, 35 mg/kg. After endotracheal intubation, artificial respiration was controlled by a Harvard respirator pump (model 607) with room air at 12 to 15 breaths/min, and blood gases and pH were analyzed at regular intervals and maintained within the following ranges: 80 to 100 mm Hg (partial pressure of oxygen), 40 to 50 mm Hg (partial pressure of carbon dioxide), and 7.35 to 7.45 (pH). Through a thoracotomy in the fifth left intercostal space, the heart was suspended in a pericardial cradle. The left anterior descending (LAD) coronary artery was dissected free immediately after the first septal perforator for subsequent occlusion. Left ventricular (LV) pressure was measured through a catheter inserted into the left ventricle through a stab wound in the apex. Catheters were also placed in both femoral arteries and in the left atrial appendage.

As shown in Figure 1, three pairs of ultrasonic crystals were implanted into the endocardial layers, perpendicularly to the long axis of the left ventricle, 1 to 2 cm apart and varying in depth from 6 to 11 mm according to LV thickness within the free wall in potentially nonischemic, moderately ischemic, and severely ischemic zones. The labelling of these zones was confirmed after completion of the experiment. The nonischemic zone was defined as the portion of the LV wall remote from the area of distribution of the occluded vessel. The severely ischemic zone was defined as the central area of distribution of the occluded vessel and showed reductions in transmural flow and function greater than 60 and 90%, respectively. The area intermediate between the severely ischemic and nonischemic areas was considered the moderately ischemic zone.

Systemic and LV pressures were measured with Hewlett-Packard 1280C transducers, and the first derivative of LV pressure (dP/dt) was obtained by electronic differentiation. A cardiotachometer, triggered by the electrocardiogram (lead II) provided instantaneous and continuous records of heart rate.

Data were recorded on a Hewlett-Packard 8800 multichannel recorder. Retroperfusion blood flow rates were measured with a 2 mm electromagnetic T probe (Statham SP 2202 flowmeter).

Diastolic synchronized retroperfusion (DSR) was achieved by using an electrocardiographically synchronized catheter-pump system (Fig. 1), which has been previously described.[5,6] Briefly, the gas-actuated DSR cardiac synchroperfusor propels arterial blood during diastole through an 8Fr autoinflatable bladder catheter.[5] The bladder of the retroperfusion catheter located in the coronary sinus was actuated directly from the central lumen of the catheter through 2 holes. The DSR catheter was specially designed to compartmentalize the coronary sinus at the onset of diastole in order to ensure unidirectional retrograde infusion of arterial blood toward the ischemic zones.[4,5] Actuation of the retroperfusion catheter is obtained from an electropneumatic console triggered by the electrocardiogram. The tip of the DSR catheter was located in the vicinity of the Marshall vein within the higher part of the coronary sinus draining the ischemic and nonischemic zones. During diastole, retroperfusion flow through the catheter lumen delivers unidirectional low pressure (45 ± 5 mm Hg) arterial blood (60 ± 10 ml/min)[5] sampled from the femoral artery. Conversely, at the onset of systole, sudden and slight reversal of flow causes rapid and total collapse of the bladder,[4] allowing venous drainage and washout of metabolites from ischemic zones.

An improved ultrasonic transit-time dimension gauge (Schuessler, Cardiff-by-the-Sea, California) was used to measure continuously instantaneous regional myocardial segment length. The miniature ultrasonic transducers were manufactured from 3 MHz piezoelectric crystals and were approximately 2 mm in diameter with a thickness of 1 mm. The location of the crystals in the endocardial layer was confirmed at autopsy. Calibration was performed by substituting pulses of precisely known duration in 1 μs increments from a crystal-controlled pulse generator with a stability of ±0.1%.

The end-diastolic point was identified as the point following the a wave of the LV end-diastolic pressure curve just before isovolumetric contraction (rapid rise in pressure), and the end-systolic point was defined as the time at which maximum negative dP/dt occurred. From the signal produced by the transit-time dimension gauge, the end-diastolic length (EDL)

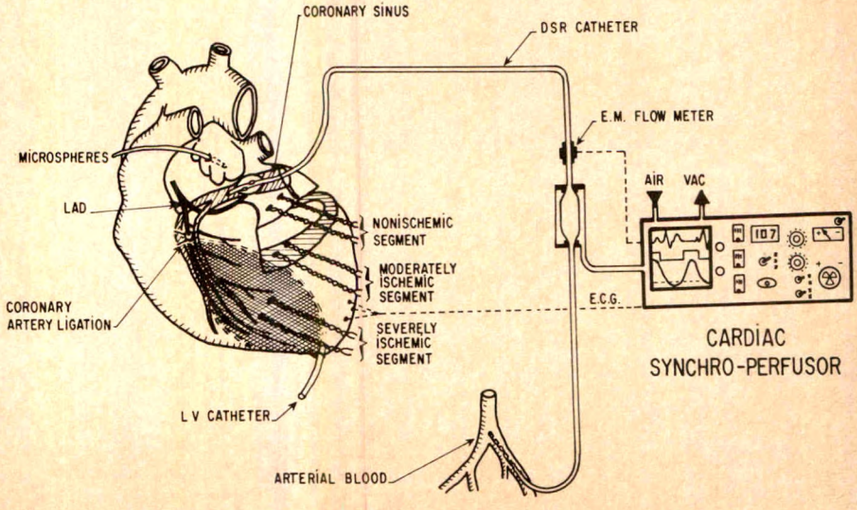

FIGURE 1. Schematic diagram of the diastolic synchronized retroperfusion experimental system. Arterial blood was shunted from a peripheral artery to the diastolic synchronized retroperfusion (DSR) catheter located in the coronary sinus. Retroperfusion was achieved by means of an air-blood unit, which was actuated by an electropneumatic cardiac synchroperfusor. The retroperfusion flow rate was monitored by an electromagnetic (EM) flowmeter probe. The **crosshatched area** indicates the zone made ischemic by left anterior descending (LAD) coronary artery occlusion. Three pairs of ultrasonic crystals were subendocardially implanted in the left ventricular wall in a circumferential plane for measurement of segment length at 3 sites: nonischemic, moderately ischemic, and severely ischemic zones. Microspheres were injected through the catheter in the left atrial appendage. ECG = electrocardiogram; LV = left ventricular; VAC = vacuum.

and end-systolic length (ESL) of the subtended myocardial segment were determined and the percent segment shortening (% ΔL) was calculated from the following formula: % ΔL = (EDL − ESL)/EDL × 100%. Each measured value was normalized to a 10 mm initial segment length by dividing the observed length by the control EDL and multiplying by 10. This method of normalizing segment dimensions was chosen because the distance between each pair of crystals was variable and arbitrarily chosen (1 to 2 cm) in relation to the actual circumference of each heart, thus making it more convenient to compare segment response among different dogs.[7,8] All data were recorded at a paper speed of 100 mm/s on the Hewlett-Packard 8800 multichannel recorder and measurements were made at end-expiration, with the respirator turned off.

Regional myocardial blood flow was measured by the radioactive microsphere technique.[9] The microspheres (New England Nuclear, Boston, Massachusetts) were suspended in 0.01% Tween® 80 solution (10% dextran) and were sonicated (50 W, Ultrasonic NSU 144 ultrasound generator) for 20 minutes and mixed by vigorous stirring with a Teflon®-covered magnet before injection. Absence of microsphere aggregation was verified by microscopic examination. Approximately 2 million microspheres (15 ± 3 μm in diameter), labelled with cerium-141, ruthenium-103, and niobium-96 suspended in 10 ml of 10% dextran, were injected through the left atrial appendage catheter for each flow determination. The choice of the radioisotope sequence was randomized. A reference sample of arterial blood was withdrawn (20 ml/min) beginning 10 seconds before microsphere injection and continuing for 80 seconds after the injection was completed. After the animal was killed, myocardial tissue samples were obtained from the sites where function had been measured. These were dissected into endocardial, mid-wall, and epicardial layers. All samples were weighed (approximately 1 to 1.5 g) and counted with appropriately selected energy windows in a gamma well counter (Compugamma, LKB Wallac, Turku, Finland). The raw counts were then corrected for background and crossover and compared with the reference blood sample to obtain flow expressed in ml/min/g of tissue. Finally, the endocardial/epicardial flow ratio was calculated.

Study protocol: The experimental protocol was conducted in 3 randomized groups of animals. In group I (n = 6), which served as the control group, LAD coronary artery ligation was maintained during 180 minutes without any further intervention. In retroperfused animals (group II [n = 7]), LAD coronary artery ligation was performed as in the control group, but synchronized retroperfusion was initiated 10 minutes after coronary occlusion and allowed to continue for 170 minutes. In reperfused animals (group III [n = 9]), the LAD coronary artery was occluded for 10 minutes and anterograde reperfusion was restored by release of the arterial ligation. In each experimental group, control measurements of LV pressure, LV dP/dt, mean aortic pressure, heart rate, and myocardial segment length shortening were obtained just before the first injection of labelled microspheres. After LAD coronary artery occlusion, hemodynamic parameters and myocardial segment length shortening were recorded at regular intervals and a second injection of microspheres was made 10 minutes after LAD occlusion when regional myocardial function and hemodynamic measurements were stable. In any event, in control animals, as well as in reperfused and retroperfused animals, hemodynamic parameters and myocardial segment length shortening were carefully recorded every 15 minutes until 170 minutes. At this time, the third injection of microspheres was performed before the animal was killed.

Results are expressed as means ± standard error of the mean (SEM). The significance of the changes produced by a given treatment from the occlusion baseline level was determined with use of Student's *t* test for paired data. Comparisons between control group and either treated group and between the 2 treated groups were done with use of a two-way analysis of variance.

TABLE I Hemodynamic Effects of 170 Minutes of Retroperfusion (n = 7) During Permanent Coronary Artery Occlusion (CAO) (180 Minutes) Compared With 180 Minutes of Control CAO (n = 6) and 170 Minutes of Reperfusion (n = 6) After 10 Minutes of CAO

Group	Preocclusion Value	10 Minutes	60 Minutes	120 Minutes	180 Minutes
			Heart Rate (beats/min)		
Control	136 ± 8	147 ± 8*	135 ± 12	136 ± 13	135 ± 12
Retroperfusion	139 ± 4	146 ± 4*	130 ± 2	119 ± 3*	115 ± 3*,†
Reperfusion	137 ± 12	150 ± 12*	139 ± 11	133 ± 10	136 ± 10
			Mean Arterial Pressure (mm Hg)		
Control	114 ± 5	109 ± 6	111 ± 6	115 ± 6	115 ± 6
Retroperfusion	106 ± 5	101 ± 6	101 ± 8	97 ± 9	100 ± 9
Reperfusion	107 ± 12	101 ± 9	107 ± 10	113 ± 10	110 ± 8
			Left Ventricular Pressure (mm Hg)		
Control	133 ± 6	130 ± 5	130 ± 7	138 ± 5	141 ± 5
Retroperfusion	123 ± 5	112 ± 7	116 ± 11	116 ± 8	115 ± 7
Reperfusion	121 ± 6	115 ± 9	120 ± 9	125 ± 10	126 ± 9
			Left Ventricular End-Diastolic Pressure (mm Hg)		
Control	4.8 ± 0.8	5.2 ± 0.6	5.2 ± 0.4	6.3 ± 0.5	5.6 ± 0.9
Retroperfusion	5.1 ± 0.6	5.6 ± 0.9	5.5 ± 0.3	4.9 ± 0.9	5.2 ± 0.6
Reperfusion	5.6 ± 0.7	6.1 ± 0.5	5.8 ± 0.8	5.7 ± 0.5	5.1 ± 0.3
			dP/dt (mm Hg/s)		
Control	2,125 ± 308	1,125 ± 216*	1,791 ± 321	1,858 ± 281	1,816 ± 231
Retroperfusion	1,816 ± 174	1,591 ± 140*	1,658 ± 118	1,653 ± 109	1,745 ± 155
Reperfusion	2,054 ± 254	1,820 ± 229*	2,108 ± 278	1,970 ± 263	2,029 ± 223

* $p < 0.05$, compared with preocclusion value.
† $p < 0.05$, effects of retroperfusion versus those of control and reperfusion.

Results

None of the retroperfusion-treated animals developed ventricular fibrillation or sustained ventricular arrhythmias, while 3 of the 9 reperfusion-treated animals developed ventricular fibrillation immediately or within a few minutes after LAD occlusion release.

Hemodynamic parameters: Table I summarizes the hemodynamic data in the 3 groups of animals. In all groups, coronary occlusion was associated with the usual transient increase in heart rate. Subsequently, heart rate decreased in the retroperfusion group ($-14 \pm 3\%$ at 120 minutes, $p < 0.01$, and $-17 \pm 4\%$ at 180 minutes, $p < 0.01$ from the preocclusion value) and was significantly lower ($p < 0.05$) than in the control and reperfusion groups at 180 minutes. Peak LV dP/dt was significantly reduced after 10 minutes of LAD occlusion in all groups and subsequently remained slightly depressed in the control group only. Mean arterial and systolic and end-diastolic LV pressures remained unaffected in the 3 groups throughout the experiment.

Regional left ventricular function: In the nonischemic zone (Fig. 2 and 3), there was no significant difference among the 3 groups in the preocclusion values of EDL, ESL, and percent segment shortening. Furthermore, during the 180 minute occlusion period, none of the regional LV function parameters in the 3 groups showed any significant change compared with its preocclusion value, and there was no difference at any time in the values of any parameter in the 3 groups.

In the moderately ischemic zone (Table II, Fig. 2 and 3), ESL and percent segment shortening in the control group were respectively increased ($+20 \pm 8\%$ of preocclusion value at 180 minutes, $p < 0.01$) and decreased ($-77 \pm 9\%$ of preocclusion value at 180 minutes, $p < 0.001$). After LAD occlusion release in the reperfusion group, all regional LV function parameters almost returned to preocclusion values within 120 minutes. In the retroperfusion group, regional LV function parameters improved steadily during the retroperfusion period, ESL and percent segment shortening values at 180 minutes being increased and decreased, respectively, by only $10 \pm 4\%$ and $-47 \pm 11\%$ compared with preocclusion values. These values, although significantly improved compared with the corresponding values in the control group, remained significantly lower than those in the reperfusion group ($p < 0.05$).

In the severely ischemic zone (Table III, Fig. 2 and 3), ESL and percent segment shortening in the control

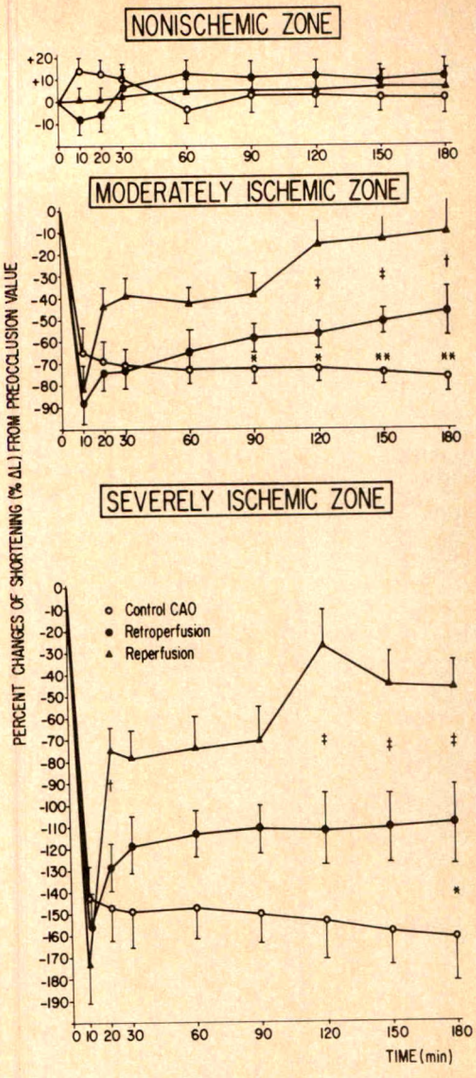

FIGURE 2. Kinetics of the percent changes (from preocclusion values) of contractile function in the nonischemic, moderately ischemic, and severely ischemic zones in the control occlusion group (**open circles**), the retroperfused group (**closed circles**), and the reperfused group (**triangles**) during the 180 minutes after coronary artery occlusion (CAO). Values for percent segment shortening have been normalized to preocclusion control values to facilitate comparison between groups. Percent changes in shortening above and below -100% refer, respectively, to active shortening and passive lengthening. * $p < 0.05$, ** $p < 0.01$, significant difference between control occlusion and retroperfused groups; † $p < 0.05$, ‡ $p < 0.01$, significant difference between retroperfused and reperfused groups.

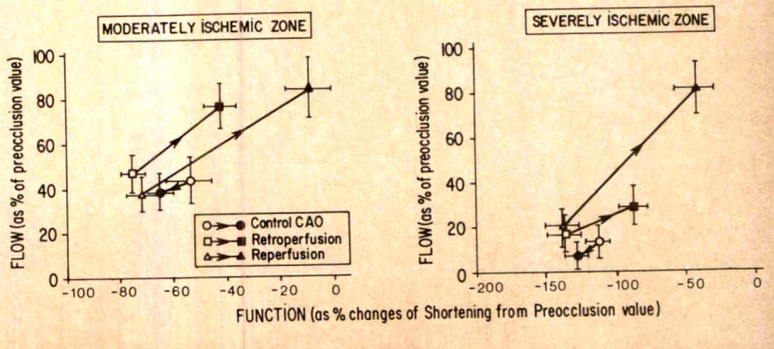

FIGURE 3. Relationship between function (percent changes in shortening from preocclusion value) and endocardial flow (percent of preocclusion flow value) changes in the moderately ischemic and severely ischemic zones. **Open symbols** correspond to flow and function values after 10 minutes of coronary artery occlusion (CAO), and **closed symbols** correspond to those observed 170 minutes later in the control occlusion group (**circles**), the retroperfused group (**squares**), and the reperfused group (**triangles**).

TABLE II Changes in Regional Myocardial Function of Moderately Ischemic Zone After 170 Minutes of Retroperfusion (n = 7) During Permanent Coronary Artery Occlusion (CAO) (180 Minutes) Compared With 180 Minutes of Control CAO (n = 6) and 170 Minutes of Reperfusion (n = 6) After 10 Minutes of CAO

	Preocclusion Value	10 Minutes	60 Minutes	120 Minutes	180 Minutes
Control Group					
End-diastolic length (mm)	10	10.56 ± 0.36	10.45 ± 0.33	10.43 ± 0.30	10.40 ± 0.34
End-systolic length (mm)	8.37 ± 0.14	9.94 ± 0.28†	9.99 ± 0.32†	9.98 ± 0.34†	10.02 ± 0.36†
Percent shortening	16.22 ± 1.40	5.67 ± 1.09†	4.29 ± 0.48†	4.31 ± 0.83†	3.61 ± 0.89†
Retroperfusion Group					
End-diastolic length (mm)	10	10.32 ± 0.20	10.63 ± 0.55	9.98 ± 0.17	9.87 ± 0.19
End-systolic length (mm)	8.10 ± 0.22	10.11 ± 0.18†	9.82 ± 0.21†	9.16 ± 0.12*,§	8.89 ± 0.15¶
Percent shortening	18.95 ± 2.22	1.98 ± 0.96†,§	6.56 ± 4.23*	8.09 ± 1.08†,§	9.91 ± 0.95†,¶
Reperfusion Group					
End-diastolic length (mm)	10	10.10 ± 0.12	9.89 ± 0.16	10.07 ± 0.16	10.06 ± 0.16
End-systolic length (mm)	8.71 ± 0.24	9.91 ± 0.25*	9.03 ± 0.16§,**	8.81 ± 0.18¶	8.73 ± 0.20¶
Percent shortening	14.80 ± 2.40	1.85 ± 1.43†,§	8.52 ± 0.94*,¶	12.49 ± 0.97¶,++	13.24 ± 1.38¶,**

* p <0.05, † p <0.01, compared with preocclusion values.
§ p <0.05, ¶ p <0.01, values of retroperfusion or reperfusion groups significantly different from corresponding value in control group.
** p <0.05, ++ p <0.01, values of reperfusion group significantly different from corresponding value in retroperfusion group.

group were respectively increased (+36 ± 9% of preocclusion value at 180 minutes, p <0.01) and decreased (−160 ± 20% of preocclusion value at 180 minutes, p <0.001) during LAD occlusion. In the reperfusion group, regional LV function began to recover gradually as early as 10 minutes after LAD occlusion release, but at 180 minutes ESL remained increased (+9 ± 2% of preocclusion value, p <0.01) and percent segment shortening decreased (−46 ± 12% of preocclusion value, p <0.001). In the retroperfusion group, regional LV function was also improved but at 180 minutes ESL remained increased (+12 ± 5% of preocclusion value, p <0.05) and percent segment shortening decreased (−108 ± 18% of preocclusion values, p <0.001).

Although on the average, paradoxical bulging persisted at 180 minutes in the retroperfusion group, it should be pointed out that 3 of the 6 dyskinetic segments at 10 minutes of LAD occlusion reverted to hypokinesia. Furthermore, percent segment shortening at 180 minutes (−1.06 ± 1.86) was significantly increased compared with the corresponding value (−7.71 ± 2.26) at 10 minutes LAD occlusion (p <0.01). Thus, as previously observed in the moderately ischemic zone, retroperfusion afforded at 180 minutes a significant improvement (p <0.05 compared with the control group) in regional LV function, but this improvement was significantly smaller (p <0.01) than that induced by reperfusion.

Regional myocardial blood flow: In the nonischemic zone (Table IV, Fig. 3 and 4), preocclusion values of transmural, endocardial, and epicardial flows and of endocardial/epicardial ratio were similar in the 3 groups. They remained unaffected by 10 minutes of LAD occulsion as well as by subsequent treatments (reperfu-

TABLE III Changes in Regional Myocardial Function of Severely Ischemic Zone After 170 Minutes of Retroperfusion (n = 7) During Permanent Coronary Artery Occlusion (CAO) (180 Minutes) Compared With 180 Minutes of Control CAO (n = 6) and 170 Minutes of Reperfusion (n = 6) After 10 Minutes of CAO

	Preocclusion Value	10 Minutes	60 Minutes	120 Minutes	180 Minutes
Control Group					
End-diastolic length (mm)	10	10.76 ± 0.39	10.84 ± 0.33	10.80 ± 0.28	10.78 ± 0.34
End-systolic length (mm)	8.57 ± 0.15	11.42 ± 0.47†	11.56 ± 0.41†	11.60 ± 0.35†	11.67 ± 0.34†
Percent shortening	14.18 ± 1.58	−6.14 ± 2.17†	−6.64 ± 1.99†	−7.51 ± 2.17†	−8.51 ± 1.98†
Retroperfusion Group					
End-diastolic length (mm)	10	9.73 ± 0.28	9.79 ± 0.34§	9.60 ± 0.36§	9.53 ± 0.36§
End-systolic length (mm)	8.62 ± 0.24	10.47 ± 0.35†	9.97 ± 0.41†,§	9.76 ± 0.43*,¶	9.64 ± 0.46*,¶
Percent shortening	13.70 ± 2.47	−7.71 ± 2.26†	−1.83 ± 2.27†	−1.57 ± 1.90†	−1.06 ± 1.86†,§
Reperfusion Group					
End-diastolic length (mm)	10	10.70 ± 0.28	10.13 ± 0.14	10.64 ± 0.11**	10.47 ± 0.16**
End-systolic length (mm)	8.96 ± 0.14	11.66 ± 0.29†	9.80 ± 0.32†,¶	9.67 ± 0.27*,¶	9.75 ± 0.27†,¶
Percent shortening	12.37 ± 1.40	−9.08 ± 1.66†	3.28 ± 2.41†,¶	9.09 ± 2.18†,¶,‡	6.77 ± 2.10†,¶,‡

* p <0.05, † p <0.01, compared with preocclusion value.
§ p <0.05, ¶ p <0.01, values of retroperfusion or reperfusion group significantly different from corresponding value in control group.
** p <0.05, ‡ p <0.01, values of reperfusion group significantly different from corresponding value in retroperfusion group.

TABLE IV Changes in Regional Myocardial Blood Flow in the Control Group (n = 6), Retroperfusion Group (n = 7), and Reperfusion Group (n = 6)

	Nonischemic Zone			Moderately Ischemic Zone			Severely Ischemic Zone		
	Preocclusion Value	10 Minutes	180 Minutes	Preocclusion Value	10 Minutes	180 Minutes	Preocclusion Value	10 Minutes	180 Minutes
Control Group									
Endo	1.02 ± 0.10	0.97 ± 0.12	0.96 ± 0.11	1.04 ± 0.12	0.45 ± 0.06†	0.38 ± 0.06†	1.06 ± 0.05	0.14 ± 0.02†	0.09 ± 0.02†
Epi	0.96 ± 0.10	0.87 ± 0.09	0.86 ± 0.10	1.13 ± 0.14	0.70 ± 0.09*	0.70 ± 0.06*	1.04 ± 0.04	0.27 ± 0.03†	0.26 ± 0.03†
Endo/epi	1.07 ± 0.07	1.12 ± 0.07	1.10 ± 0.05	0.96 ± 0.08	0.63 ± 0.08*	0.55 ± 0.09*	1.02 ± 0.05	0.58 ± 0.09†	0.34 ± 0.04†
Retroperfusion Group									
Endo	1.03 ± 0.07	0.93 ± 0.06	0.93 ± 0.03	0.93 ± 0.05	0.58 ± 0.05†	0.70 ± 0.06*,§,++	0.97 ± 0.04	0.16 ± 0.02†	0.28 ± 0.05†,§,++,¶¶
Epi	0.99 ± 0.10	0.90 ± 0.07	0.96 ± 0.03	0.92 ± 0.08	0.76 ± 0.07*	0.83 ± 0.06*	0.94 ± 0.03	0.38 ± 0.04†	0.48 ± 0.04†,§,++,¶¶
Endo/epi	1.08 ± 0.07	1.03 ± 0.04	0.97 ± 0.04	1.01 ± 0.04	0.77 ± 0.04*	0.84 ± 0.03*,§,‡	1.04 ± 0.03	0.41 ± 0.05†	0.57 ± 0.08†,§,++,¶¶
Reperfusion Group									
Endo	1.16 ± 0.13	0.99 ± 0.08	1.03 ± 0.18	1.09 ± 0.13	0.41 ± 0.05†	0.90 ± 0.11¶,‡	1.13 ± 0.10	0.21 ± 0.04†	0.93 ± 0.12¶,‡
Epi	1.14 ± 0.09	1.06 ± 0.08	1.08 ± 0.15	1.04 ± 0.10	0.50 ± 0.03†	0.85 ± 0.12*,¶,++	1.12 ± 0.09	0.30 ± 0.04†	1.01 ± 0.09¶,‡
Endo/epi	1.02 ± 0.06	0.94 ± 0.03	0.93 ± 0.06	1.02 ± 0.05	0.79 ± 0.06†	0.94 ± 0.10¶,‡	1.01 ± 0.03	0.49 ± 0.06†	0.91 ± 0.04¶,‡

* $p < 0.05$, † $p < 0.01$, compared with preocclusion value.
§ $p < 0.05$, ¶ $p < 0.01$, compared with corresponding value at 10 minutes of coronary occlusion.
++‡ $p < 0.05$, ‡ $p < 0.01$, values of retroperfusion and reperfusion group significantly different from corresponding value in control group.
¶¶ $p < 0.05$, values of retroperfusion group compared with corresponding value in reperfusion group.

FIGURE 4. Transmural myocardial blood flow in the nonischemic, moderately ischemic, and severely ischemic zones in the control occlusion group (**Left open bars**), in the retroperfused group (**shaded bars**) and in the reperfused group (**right open bars**) before and after 10 minutes of coronary artery occlusion (CAO) and 170 minutes later. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, significant difference from the preocclusion value; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$, significant difference from the 10 minute coronary artery occlusion value.

sion, retroperfusion, or permanent occlusion for 170 minutes).

In the moderately ischemic zone, transmural flow decreased to approximately 53% of its initial value after 10 minutes of LAD occlusion in the 3 groups. This reduction affected the endocardium more markedly than the epicardium, leading to a significantly reduced endocardial/epicardial ratio (approximately 28% of its initial value) in the 3 groups. Transmural, endocardial, and epicardial flows and endocardial/epicardial ratio values were not further modified at 180 minutes in the control group. Reperfusion induced an almost complete recovery in all flow parameters. Transmural flow increased significantly to a value which at 180 minutes no longer differed from the preocclusion one. This increase was more marked in the endocardium than in the epicardium, leading to a significant increase in the endocardial/epicardial ratio to a value which at 180 minutes no longer differed from the preocclusion one. Retroperfusion also significantly increased transmural flow but the value reached at 180 minutes, although not significantly different from the corresponding one in the reperfusion group, remained significantly lower than the preocclusion one. The endocardial/epicardial ratio value was also significantly increased by retroperfusion but

remained significantly lower than the preocclusion value.

In the severely ischemic zone, transmural flow values decreased to approximately 30% of their initial values after 10 minutes of LAD occlusion in the 3 groups. This reduction again affected the endocardium more markedly than the epicardium, leading to a significantly reduced endocardial/epicardial ratio (approximately 50% of its initial value) in the 3 groups. In the control group, there was a slight further reduction in flows and endocardial/epicardial ratio values at 180 minutes of LAD occlusion. Reperfusion induced an almost complete recovery in all flow parameters, and transmural, epicardial, and endocardial flows as well as endocardial/epicardial ratio values at 180 minutes did not differ from preocclusion values. Retroperfusion also significantly increased transmural flow (47 ± 7% of the initial value at 180 minutes versus 30 ± 8% of the initial value at 10 minutes, $p < 0.05$), but the value reached at 180 minutes remained significantly ($p < 0.001$) lower than the preocclusion one. However, this increase was more marked in the endocardium than in the epicardium, leading at 180 minutes to an increased endocardial/epicardial ratio compared with 10 minutes ($p < 0.05$), but the value reached at 180 minutes remained significantly lower than the preocclusion one ($p < 0.001$). Thus, retroperfusion induced a significant improvement in regional flows and endocardial/epicardial ratio values compared with the control group ($p < 0.05$), but this improvement remained significantly smaller ($p < 0.001$) than that induced by reperfusion.

Discussion

The results of the present study indicate that diastolic synchronized retroperfusion has beneficial effects on regional myocardial blood flow and function in open-chest dogs with a permanent 3 hour LAD occlusion. In order to adequately evaluate the potential regional benefits of coronary sinus retroperfusion starting 10 minutes after coronary occlusion, we compared over 170 minutes its simultaneous effects on regional myocardial blood flow and regional function to those induced either by restoration of anterograde flow after 10 minutes of coronary artery ligation alone or by maintained coronary artery ligation for 180 minutes (control group). LAD occlusion results in major ultrastructural, biochemical, and functional myocardial alterations[7,10–14] the recovery from which has been shown to be primarily dependent upon the duration of the ischemic period.[15] Therefore, in the reperfused animals, the duration of the LAD occlusion was short enough (10 minutes) to avoid irreversible myocardial necrosis and thus possibly allow a large recovery in all measured parameters. In the 2 other groups (control and retroperfused animals), coronary artery ligation lasted 180 minutes and was likely to induce comparable impairments in regional myocardial blood flow and contractile function. Furthermore, it was previously shown in dogs that these impairments rapidly reach a steady state.[12] Thus, in the ischemic zones, endocardial and epicardial flows are stable up to 2 hours after occlusion,[12] epicardial flow being only slightly increased after 6 hours.[16] Regarding contractility, ischemic myocardium begins to contract abnormally within seconds after coronary occlusion and exhibits paradoxical bulging if ischemia is severe enough.[7,8,12] However, these alterations are stable within 5 minutes and no further changes occur until 24 hours after occlusion.[12,13] This stability in regional flow and function impairments is clearly confirmed by the present study in our control group. Finally, it must be stressed that a close relationship between regional blood flow reduction and myocardial functional impairment, especially at the endocardial level, has been demonstrated in both anesthetized[17–21] and conscious dogs.[22]

The effectiveness of coronary sinus retroperfusion in partially reversing the effects of ischemia in moderately and severely ischemic zones is clearly demonstrated in this study. In moderately ischemic zones, retroperfusion was almost as effective as reperfusion in restoring transmural flow and endocardial/epicardial ratio values since the latter were not significantly different in the 2 groups at the end of the experiment. However, as shown in Figure 3, for the same increment in endocardial flow, retroperfusion-induced improvement in contractile function, which resulted in a restoration of 50% of the initial contractility, was significantly smaller than that induced by reperfusion. In the severely ischemic zone, retroperfusion increased transmural blood flow back to 47% of its preocclusion value, significantly increased the endocardial/epicardial ratio value, and significantly improved function compared with the control group; 3 of 6 segments exhibiting paradoxical bulging after 10 minutes of occlusion reverted to hypokinesia. However, these beneficial effects of retroperfusion remained significantly smaller than those induced by reperfusion, which completely restored regional myocardial blood flow and endocardial/epicardial ratio values and induced a 50% recovery in contractility, in agreement with previous data.[10,15] Thus, in both moderately and severely ischemic zones, retroperfusion significantly improved regional myocardial blood flow and function compared with that in the control group, but its beneficial effects were generally smaller than those of anterograde perfusion.

The retroperfusion-induced improvement in severely ischemic zone contractility cannot be accounted for by changes in the LV loading conditions since neither preload as reflected by nonischemic left ventricular end-diastolic length nor afterload as reflected by left ventricular systolic pressure were modified even if a slight but significant bradycardia occurred simultaneously. It also cannot be due to decrease in regional compliance since (1) left ventricular end-diastolic pressure was unchanged during retroperfusion, (2) no trend toward such a decrease in compliance was observed in the control group, and (3) the onset of the decrease in compliance has been shown not to occur at least before 7 hours after coronary occlusion. Moreover, the improvement in regional function with diastolic synchronized retroperfusion was not artifactual (that is, an "erectile effect" related to the diastolic pumping of the myocardium) since (1) the amount of blood at each diastolic stroke was small, and (2) the improvement in segmental function occurred gradually throughout the retroperfusion period and was of dif-

ferent magnitude in the moderately and severely ischemic zones. Thus, it is very likely that the beneficial effects of retroperfusion on regional contractility are related primarily to the improvement in local flows and in the endocardial/epicardial ratio, as previously suggested.[3,4,6]

It was recently shown that myocardial necrosis is directly proportional to the severity of ischemia when regional blood flow is reduced below 70 to 75% of control flow.[13] Furthermore, linear relationships between the extent of histologic necrosis and the reduction in regional blood flow measured at any time after complete coronary artery occlusion have been well documented.[17,23] Accordingly, restoring approximately 50% of preocclusion flow in the ischemic area may be expected to result in a substantial reduction of the ultimate infarct size provided coronary sinus retroperfusion is initiated early enough after coronary artery occlusion. This concept is further supported by the recent report by Smith et al[24] demonstrating that a 4 hour retroperfusion period during LAD occlusion followed by anterograde reperfusion results in a mean reduction of 84% in ultimate histologic infarct size. Finally, it must be remembered that the values of regional myocardial blood flow reported here after retroperfusion underestimate the actual enhancement of flow within the retroperfused zones since, as we showed previously,[6] 8 to 12% of the microspheres used to assess flow escape through venovenous and thebesian channels during the procedure.

The favorable redistribution of retroperfused arterial blood to the subendocardium previously reported[6] and confirmed in the present investigation suggests that coronary sinus retroperfusion might benefit the whole salvageable border zone. Preservation of subendocardium would be of major importance since it was recently shown that the contribution of subendocardial layers to the overall LV function is far more important than that of subepicardial layers during myocardial ischemia.[25]

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Effects of Ortho-Iodo Sodium Benzoate on Acute Myocardial Ischemia, Hemodynamic Function, and Infarct Size After Coronary Artery Occlusion in Dogs

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Ortho-iodo sodium benzoate (OISB) decreases the affinity of blood for oxygen, thus enhancing potential tissue oxygen delivery. To test the hypothesis that a change in oxygen affinity would ameliorate regional myocardial ischemic injury resulting from occlusion of the left anterior descending (LAD) coronary artery, experiments were carried out in 55 anesthetized dogs which received an intravenous infusion of OISB. In Protocol I studies (n = 9), preocclusion intravenous infusion of OISB (500 mg/kg) reduced epicardial S-T segment elevation 15 minutes after coronary occlusion, while a similar volume of normal saline solution did not affect this index of ischemic damage. In Protocol II experiments, 34 dogs were randomized to either an OISB or saline group, after which the LAD was ligated, the chest closed, and the animal allowed to recover from anesthesia. Myocardial infarction (MI) size was assessed after the animal died or was killed 8 to 24 hours later, and was found to be 29% smaller in dogs receiving OISB. In 6 dogs, blood P_{50} (the partial oxygen pressure at which hemoglobin is 50% saturated with oxygen) was increased by OISB infusion, confirming that its administration effected a rightward shift in the oxyhemoglobin dissociation curve. Protocol III studies assessed the effects of OISB on cardiac hemodynamic function and acute myocardial ischemic damage when infusion was begun 15 minutes after LAD occlusion: average epicardial S-T segment elevation was not altered by saline solution, but decreased when OISB was infused during the last 15 minutes of myocardial ischemia. Reductions in heart rate, left ventricular dP/dt, and cardiac output were observed in 7 dogs during OISB infusion, but there were no changes in these measurements during coronary occlusion in 5 dogs receiving a constant infusion of saline solution. There were no changes in regional myocardial blood flow (microsphere technique) to either ischemic or nonischemic zones in either the saline control or OISB treatment groups.

Thus, both acute myocardial ischemic injury (assessed by epicardial electrocardiographic mapping) and ultimate MI size are reduced when OISB is infused before experimental coronary artery occlusion. OISB also reduces myocardial ischemic injury when its administration is begun 15 minutes after coronary occlusion, while effecting decreases in heart rate, left ventricular contractility, and cardiac output.

Various pharmacologic interventions are known to ameliorate acute myocardial ischemic injury and reduce infarct size in animal models of acute myocardial infarction (MI).[1,2] Some are thought to partially correct the imbalance between myocardial oxygen supply and demand in ischemic myocardium.[3] For example, beta-adrenergic blockade may decrease heart rate and contractile force, thus reducing the demand for oxygen.[4] Alternatively, coronary vasodilators may improve collateral blood flow to the ischemic zone,[5] or coronary reperfusion may reduce ischemic damage[6,7] as it restores subepicardial blood flow to nearly normal levels.[8]

Few interventions, other than those which actually increase the *volume* of blood flow to ischemic myocardium, are available to improve myocardial oxygen supply. Accordingly, we postulated that ortho-iodo sodium benzoate (OISB), a benzoic acid derivative which decreases the affinity of hemoglobin for oxygen, thus enhancing potential tissue oxygen delivery,[9–11] might ameliorate acute myocardial ischemic damage after coronary artery occlusion. This report presents

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data on the effects of OISB on acute myocardial ischemia and hemodynamic function in the barbiturate-anesthetized dog, and on ultimate MI size after permanent coronary artery ligation.

Methods

General methods: Fifty-five mongrel dogs of both sexes, weighing 17 to 30 kg, were anesthetized with intravenous thiamylal (20 mg/kg), intubated with a cuffed endotracheal tube, and ventilated with room air through a Harvard respirator. A thoracotomy was performed through the fifth left intercostal space, and the heart was suspended in a pericardial cradle. A lead II electrocardiogram and calibrated femoral or carotid arterial pressure were recorded on a multichannel physiologic recorder (Gould Brush Recorder model 1707). In selected dogs, the left atrium was cannulated with a polyethylene catheter for the administration of radioactive microspheres, and a micromanometer-tipped catheter (Millar Instruments model P1470) was inserted into the left ventricular chamber, either retrogradely through a carotid entry site, or directly through the apex of the left ventricle. The peak rate of rise of left ventricular pressure (LV dP/dt) was determined at end-expiration with the aid of an electronic differentiator (Biotronix Laboratory model 620).

In each dog, a portion of the left anterior descending (LAD) coronary artery was dissected free so that either temporary coronary occlusion (with a Schwartz arterial clamp) or permanent coronary ligation (with a 4-0 silk suture) could be performed. In dogs undergoing temporary coronary occlusion, either the mid-portion of the LAD or the proximal part of its major diagonal branch was chosen as the site for coronary occlusion. In animals undergoing permanent coronary ligation, the proximal portion of the LAD artery was occluded.

Epicardial electrocardiography: Epicardial electrograms were recorded during temporary coronary occlusion as follows: a soft cotton wick, soaked in physiologic saline solution, was impacted into a hollow copper cylinder 4 mm in diameter, and this apparatus was applied to predetermined epicardial sites recognized by their relation to epicardial arteries and veins. A unipolar electrogram was recorded (sensitivity of 1 mV/mm and paper speed 25 mm/s) through a standard electrocardiographic amplifier.[1] Ischemic sites for electrocardiographic recordings were chosen from areas judged to be perfused by the branch chosen for coronary occlusion. Areas adjoining the sites of dissection of the coronary artery or placement of catheters were avoided for mapping purposes because of the possibility of traumatic epicardial injury; similarly, animals requiring defibrillation were excluded because of the possibility of epicardial injury by electrical countershock. The magnitude of S-T segment elevation above the T-P segment 0.04 second after the end of the QRS complex was assessed. Sites were excluded from analysis if intraventricular conduction delay (QRS duration exceeding 0.065 second) developed, because of the invalidation of epicardial S-T segment elevation as an index of ischemia by this conduction alteration.[12] Results are expressed as $\overline{ST}$ (the average S-T segment elevation [mV] per site) at timed measurement points.

Radioactive microsphere techniques[13–15]: Regional myocardial blood flow (RMBF) and cardiac output (CO) were measured by the microsphere technique in 10 Protocol III experiments (see later). Radioactive polystyrene microspheres (9 ± 1 μm in diameter) labelled with gamma emitters (Sn^{113}, Co^{57}, Ce^{141}, Sc^{46}) were suspended with 0.2% Tween®-80 in a 50% sucrose solution, and were sonicated and agitated manually immediately before use. Approximately 2×10^6 microspheres were injected into the left atrium over 15 seconds during simultaneous withdrawal of an arterial reference sample by a Harvard syringe pump. After the animal was killed, myocardial samples from the ischemic zone and the posterolateral (nonischemic) left ventricular free wall were excised and divided into subepicardial and subendocardial halves weighing 0.5 to 1.8 g. The radioactivity of injectate standards, arterial reference samples, and myocardial tissue were measured in a gamma well counter, and after correction for background radiation and spectral overlap, RMBF was calculated as $RMBF = (C_m \times RF)/(C_r \times Wt)$, where C_m = counts in each myocardial sample, RF = arterial reference sample flow rate (15.3 ml/min), C_r = counts in the reference sample, and Wt = sample weight (g).[14] The results of calculated flow from 2 or 3 nonischemic sites were averaged and expressed as the normal epicardial and subendocardial flow for each animal. Tissue from all sites demonstrating ischemic S-T segment elevation was analyzed and a weighted average transmural ischemic zone flow was calculated on the basis of the 2 to 5 sites (2 in 1 experiment; 3 in 2 dogs; 4 in 6 dogs; 5 in 1 dog) sampled in each dog. Also, RMBF was calculated for the subepicardial and subendocardial central ischemic zone (that site demonstrating maximum S-T segment elevation). Cardiac output (systemic blood flow) was calculated from microsphere data as $C.O. = C_i \div (C_r/RF)$, where C_i = the number of counts injected.[13,15]

Infarct size determination: In dogs undergoing MI size measurements, the left ventricle was dissected from the remainder of the heart and great vessels, and cut in "breadloaf" fashion into 7 to 10 mm slices in a plane parallel to the atrioventricular groove. To delineate the area of infarction, tissue slices were incubated for 30 minutes in triphenyl tetrazolium chloride (TTC) at 37°C; this lactic dehydrogenase stain makes normal myocardial tissue stain a brick red and leaves necrotic myocardium unstained.[16–18] The changes in color produced by TTC staining are closely related to the pathologic changes of myocardial necrosis, and reliably differentiate necrotic and viable myocardium as early as 6 hours after coronary occlusion.[17] Infarcted and normal tissue in each slice was then separated by sharp dissection, and infarct size was expressed as a percentage of the left ventricle by weight. Also the distance between the left coronary ostium and the site of coronary ligation was measured by an intracoronary probe. For these determinations, the investigator performing infarct size measurements was blinded as to the treatment status of the animal.

Preparation of OISB and measurement of P_{50}: OISB was prepared for intravenous administration by the method of Litwin et al.[10] Briefly, 50 g of o-iodo-benzoic acid (Eastman Kodak, Rochester, New York) was dissolved in acetone, cooled on ice, and mixed with 8.1 g of NaOH dissolved in distilled water. The o-iodo sodium benzoate precipitate was washed with cold acetone, dessicated, and dissolved to a concentration of 225 mg/ml in sterile normal saline solution. Immediately before use, the pH of the solution was adjusted to a range of 7.40 to 7.60 by addition of HCl or NaOH.

Hemoglobin-oxygen dissociation curves on heparinized arterial blood samples were performed on a Duvelleroy dissociation curve analyzer by methods previously described.[19] P_{50}, the partial oxygen pressure (pO_2) at which hemoglobin is 50% saturated with oxygen, was noted both before and 15 minutes after administration of OISB in 6 dogs.

Experimental protocols: *Protocol I* experiments were designed to determine whether OISB affected acute myocardial ischemic injury assessed by epicardial S-T segment elevation when the agent was infused before temporary coronary occlusion. Nine animals underwent electrocardiographic mapping before and at the end of two 15-minute temporary LAD occlusions separated by 1 hour of coronary reperfusion. During the 15 minutes before the second occlusion, either

OISB (500 mg/kg, 5 dogs) or an equal volume of normal saline solution (n = 4) was infused. The average S-T segment elevation at 15 minutes after the first and second occlusion was compared in both the OISB and normal saline (control) groups.

Protocol II experiments were performed to assess the effects of pretreatment with OISB on anatomically determined infarct size after permanent coronary artery occlusion. After a transient 15-second LAD occlusion confirmed that at least two thirds of the circumference of the cardiac apex was involved by epicardial cyanosis, 34 dogs were randomized by the envelope method to treatment and control groups, and received either OISB (500 mg/kg) or an equal volume of normal saline solution over the 15 minutes preceding permanent coronary ligation. The chest was then closed, the pneumothorax was evacuated, and the dogs were allowed to awaken. Both treatment and control groups received 1 liter of normal saline solution intravenously over the first 8 postoperative hours. Infarct size was measured by the TTC technique either after the animal was killed 24 hours after coronary ligation, or after spontaneous death if it occurred at least 8 hours after coronary occlusion.[16–18]

Protocol III experiments were designed to assess (1) the effects on ischemic epicardial S-T segment elevations of OISB infusion begun after the onset of myocardial ischemia, and (2) effects of OISB on cardiac hemodynamic function (heart rate, arterial pressure, cardiac output, LV dP/dt, RMBF) during LAD occlusion. Twelve anesthetized dogs underwent 30-minute LAD occlusions and received normal saline solution (50 ml) intravenously by constant infusion during the first 15 minutes of ischemia. Thirteen minutes after LAD occlusion, the foregoing hemodynamic measurements were begun, and ischemic zone epicardial S-T segment mapping was carried out. From 15 through 30 minutes after coronary occlusion, dogs received either OISB, 500 mg/kg (treatment group, n = 7), or an equal volume of normal saline solution (control group, n = 5) by constant infusion, and hemodynamic measurements were repeated 28 to 30 minutes after LAD occlusion. Indexes of ischemic severity and hemodynamic function from the first 15-minute period were then compared with those after 30 minutes of myocardial ischemia, either at the end of OISB (treatment group) or normal saline (control group) infusion.

Statistical methods[20]: All group data are presented as the mean ± 1 standard error of the mean (SEM). Comparisons of average epicardial S-T segment elevations (Protocol I), pre- and post-OISB blood P_{50} values, cardiac output and regional myocardial blood flow data (Protocol III) were performed by Student's *t* test for paired comparisons. Intergroup comparisons of preocclusion hemodynamic variables, distance from coronary ostium to site of LAD ligation, and infarct size (Protocol II) were made using Student's *t* test for unpaired data. Comparisons of serial S-T segment elevations and hemodynamic measurements (Protocol III) were performed by an analysis of variance for repeated measures, followed by the Student-Newman-Keuls multiple range test. For all comparisons, a 2-tailed p value <0.05 was required for inference of statistical significance.

Results

Protocol I: Average S-T segment elevation at ischemic sites 15 minutes after coronary occlusion ($\overline{ST}_{15}$) in dogs receiving either normal saline solution or OISB are displayed in Figure 1. $\overline{ST}_{15}$ did not change in the 4 dogs receiving normal saline solution before the second ischemic period, being 3.4 ± 0.7 mV for both coronary occlusions. However, the 5 dogs receiving OISB before the second occlusion demonstrated a marked decrease in $\overline{ST}_{15}$ from 3.7 ± 0.3 mV to 1.1 ± 0.4 mV for the 2 occlusions, respectively ($p < 0.001$).

Protocol II: Of 59 dogs with an acceptable extent of left ventricular cyanosis after transient coronary occlusion, 2 died before randomization, and 23 (12 in control group, 11 in OISB treatment group) died within 8 hours of randomization. Protocol II measurements were performed in the 34 remaining dogs. Twenty (7 OISB and 13 control) of these 34 dogs survived for 24 hours; 14 (9 OISB, 5 control) died 8 to 24 hours after coronary occlusion (no significant difference by chi-square testing).

There was no difference in preocclusion hemodynamic variables (after equal volumes of OISB or saline were infused) between control and OISB-treated dogs. Specifically, heart rate was 149 ± 4 and 139 ± 5 beats/min in the control (n = 18) and OISB (n = 16) groups,

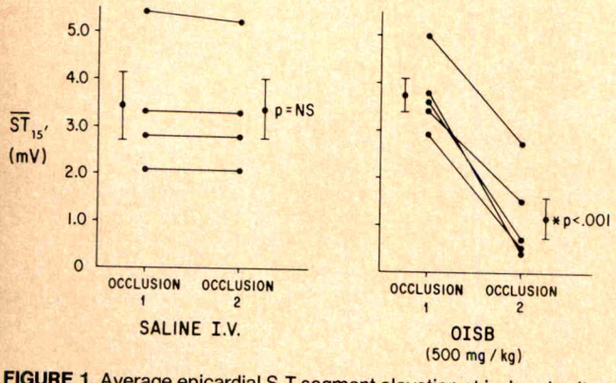

FIGURE 1. Average epicardial S-T segment elevation at ischemic sites 15 minutes after coronary occlusion ($\overline{ST}_{15'}$) is presented for serial coronary occlusions in 5 dogs receiving o-iodo sodium benzoate (OISB) before the second occlusion (**right panel**), and in 4 control dogs receiving an equal volume of normal saline before the second occlusion (**left panel**). **Bars** represent means ± standard error of the mean. I.V. = intravenous; NS = not significant.

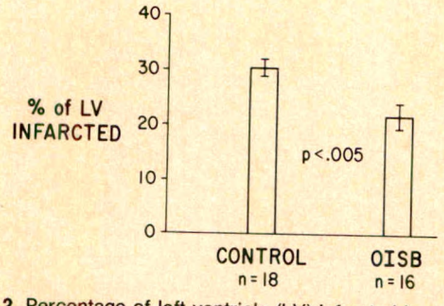

FIGURE 2. Percentage of left ventricle (LV) infarcted in control and treatment groups of dogs undergoing permanent ligation of the left anterior descending coronary artery (Protocol II). Infarct size was determined by a triphenyl tetrazolium chloride staining technique. **Bars** represent means ± standard error of the mean. Infarct size was significantly smaller ($p < 0.005$) in the treatment than in the control group (21.7 ± 2.3% and 30.5 ± 1.5% of the left ventricle for the 2 groups, respectively). n = number of animals in each group; OISB = o-iodo sodium benzoate.

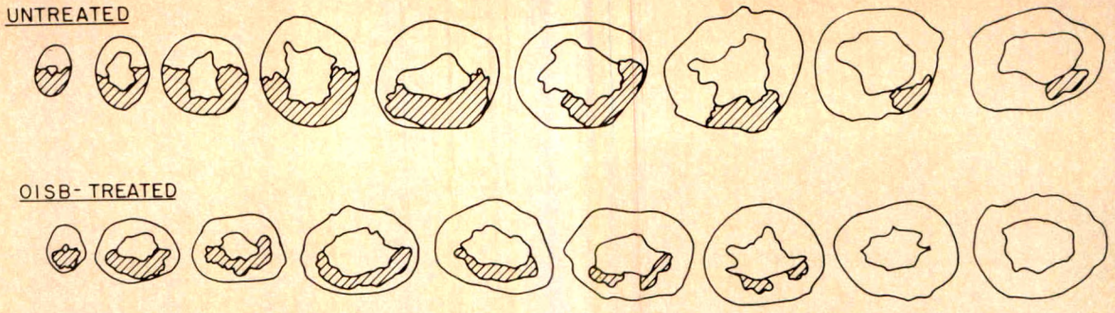

FIGURE 3. Drawings of upper (cranial) surfaces of serial transverse sections of the left ventricle below the level of left anterior descending coronary artery ligation in 2 representative dogs from Protocol II. Infarcted areas are denoted by **cross-hatching;** areas which stained normally with triphenyl tetrazolium chloride are **unshaded.** The progression of sections is from cardiac apex **(far left)** to that section including the site of coronary ligation **(far right).** The control (untreated) dog developed a large (24% of left ventricle) transmural infarction, while the dog receiving o-iodo sodium benzoate (OISB) developed a smaller (9% of left ventricle), largely nontransmural infarction.

respectively; mean arterial pressure was also similar, being 127 ± 4 and 129 ± 3 mm Hg for the 2 groups, respectively. Confirmation that the randomization process resulted in similar populations was reflected by the fact that the distance from the coronary ostium to the site of LAD ligation was similar in the 2 groups, being 2.4 ± 0.1 and 2.3 ± 0.1 cm for the control and OISB groups, respectively.

Figure 2 demonstrates the differences in infarct size between the 2 treatment groups as determined by the TTC technique. The 16 OISB-treated dogs had infarcts averaging only 21.7 ± 2.3% of the left ventricle, while control animals had an average infarct size of 30.5 ± 1.5% of the left ventricle. This 29% decrease in infarct size in the OISB group is statistically significant ($p < 0.005$). Figure 3 depicts infarcted and viable myocardium in selected dogs from the 2 treatment groups.

P_{50} measurements: In order to confirm the previously reported effects of OISB on blood oxygen affinity in the animal preparation used in these studies, arterial blood samples from 6 anesthetized dogs in Protocols I and II were obtained immediately before and 15 minutes after infusion of OISB (before coronary occlusion), and P_{50} was determined from hemoglobin-oxygen dissociation curves. P_{50} was increased by OISB infusion from 31.9 ± 0.5 to 35.7 ± 0.7 mm Hg ($p < 0.01$) (Fig. 4).

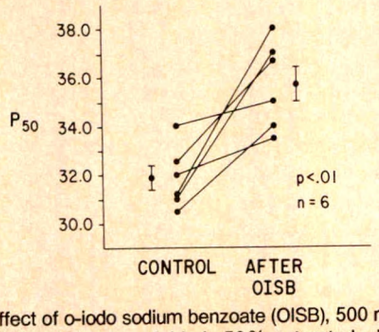

FIGURE 4. Effect of o-iodo sodium benzoate (OISB), 500 mg/kg, on P_{50} (pO_2 of blood at which hemoglobin is 50% saturated with oxygen) is shown in 6 dogs selected from Protocols I and II. P_{50} increased in each dog from control values of 31.9 ± 0.5 (standard error of the mean) to 35.7 ± 0.7 mm Hg after OISB ($p < 0.01$). Bars represent means ± 1 standard error of the mean.

Protocol III (Table I): OISB produced significant changes in hemodynamic variables and epicardial S-T segment elevations when it was infused 15 to 30 minutes after the onset of coronary occlusion (Table IA). The heart rate decreased from 164 ± 6 beats/min after the first 15 minutes of myocardial ischemia to 140 ± 7 beats/min after OISB infusion ($p < 0.001$). Left ventricular dP/dt was similar before and 15 minutes after coronary occlusion (2,224 ± 218 and 2,143 ± 204 mm Hg/s, respectively), but fell significantly (to 1,511 ± 127 mm Hg/s, $p < 0.01$ versus both previous measurement points) after 15 minutes of OISB infusion. There were no significant changes in systolic, diastolic, or mean arterial pressures throughout the study. Cardiac output decreased from 3.7 ± 0.5 liters/min after the first 15 minutes of ischemia to 2.4 ± 0.4 liters/min after OISB infusion ($p < 0.001$). There was a trend toward lower subepicardial and subendocardial myocardial blood flow to nonischemic tissue after OISB infusion, but this was not statistically significant ($0.05 < p < 0.10$). There were no differences in subepicardial or subendocardial central ischemic zone blood flows, or in transmural ischemic zone flows between the 2 measurement points. $\overline{ST}$ increased from 0 to 3.94 ± 0.58 mV ($p < 0.001$) at 15 minutes after occlusion, and decreased dramatically to 1.23 ± 0.43 mV ($p < 0.001$) after OISB infusion.

In order to confirm the stability of hemodynamic and electrocardiographic measurements in dogs undergoing coronary occlusion for the same period of time without OISB infusion, experiments were conducted in 5 control animals which received normal saline solution in volumes equivalent to the total of saline solution and OISB administered in the treatment group throughout the 30 minutes of ischemia. Results of these experiments are presented in Table IB. There were no significant changes in heart rate, arterial pressures, LV dP/dt, cardiac output, or regional myocardial blood flow to normal and ischemic zones between any of the measurement points. $\overline{ST}$ was similarly increased at 15 and 30 minutes after coronary occlusion (2.46 ± 0.38 and 2.44 ± 0.52 mV, respectively).

TABLE I Protocol III: Hemodynamic and Electrocardiographic Results

	0′	15′	30′
A. OISB Treatment Group			
HR (beats/min)	167 ± 5	164 ± 6	140 ± 7*†
SAP (mm Hg)	133 ± 5	128 ± 5	120 ± 13
DAP (mm Hg)	105 ± 5	100 ± 5	96 ± 11
MAP (mm Hg)	116 ± 5	112 ± 5	105 ± 11
LV dP/dt (mm Hg/s)	2,224 ± 218	2,143 ± 204	1,511 ± 127*†
CO (liters/min))	. . .	3.7 ± 0.5	2.4 ± 0.4†
RMBF (ml/min/g)			
Normal epi	. . .	1.47 ± 0.34	0.80 ± 0.06
Normal endo	. . .	1.46 ± 0.19	1.07 ± 0.10
Cent isch epi	. . .	0.31 ± 0.14	0.37 ± 0.12
Cent isch endo	. . .	0.12 ± 0.06	0.17 ± 0.06
Trans isch	. . .	0.21 ± 0.07	0.21 ± 0.09
Mean S-T elevation (mV)	0	3.94 ± 0.58*	1.23 ± 0.43*†
B. Control Group			
HR (beats/min)	138 ± 12	137 ± 9	141 ± 12
SAP (mm Hg)	141 ± 8	133 ± 5	142 ± 8
DAP (mm Hg)	115 ± 9	110 ± 7	117 ± 7
MAP (mm Hg)	128 ± 9	123 ± 6	127 ± 8
LV dP/dt (mm Hg/s)	3,318 ± 766	3,316 ± 706	3,240 ± 487
CO (liters/min)	. . .	3.2 ± 0.6	3.2 ± 0.9
RMBF (ml/min/g)			
Normal epi	. . .	1.02 ± 0.11	0.94 ± 0.11
Normal endo	. . .	1.23 ± 0.08	1.21 ± 0.13
Cent isch epi	. . .	0.43 ± 0.04	0.48 ± 0.08
Cent isch endo	. . .	0.13 ± 0.03	0.17 ± 0.09
Trans isch	. . .	0.27 ± 0.03	0.33 ± 0.08
Mean S-T elevation (mV)	0	2.46 ± 0.38*	2.44 ± 0.52*

All dogs received 50 ml normal saline solution (NS) by constant infusion during the first 15 minutes after coronary artery occlusion. During the second 15 minutes of the same coronary occlusion, the treatment group (Part A) received o-iodo sodium benzoate (OISB), 500 mg/kg by constant infusion, while the control group (Part B) received an equal volume of NS. Data columns represent measurements before coronary occlusion (0′), at the end of NS infusion (15′), and at the end of the 30-minute occlusion (30′). Data are presented as means ± 1 standard error of the mean, and represent experiments in 7 treatment group dogs and 5 control group dogs, except for left ventricular dP/dt (LV dP/dt), where n = 5 in the OISB group and 4 in the control group, and regional myocardial blood flow (RMBF) and cardiac output (CO), when n = 6 for the treatment group and 4 for the control group.

* $p < 0.01$ versus 0′; † $p < 0.01$ versus 15′. More exact notation of p values for selected comparisons is given in the text. Cent isch = central ischemic zone; Endo = subendocardium; Epi = subepicardium; HR = heart rate; SAP, DAP, and MAP = systolic, diastolic, and mean arterial pressures, respectively; Trans isch = weighted average transmural blood flow for all ischemic tissue sampled.

Discussion

During a systematic investigation of the in vitro effects of benzoic acid derivatives on the oxyhemoglobin dissociation curve, Laver et al[9,21] found that ortho-iodo sodium benzoate was as effective as other members of this class of agents in reducing the affinity of oxygen for hemoglobin (increasing P_{50}) and that this compound was unique in this chemical series because of the absence of undesirable effects on red cell morphologic features, rheologic features, and intracellular electrolytes and pH. They also found that the increased P_{50} observed with OISB was possible in the absence of 2,3-diphosphoglycerate. Subsequent work by Gross et al[11] revealed in vitro and in vivo elevation of P_{50} in canine blood and significant elevation of P_{50} without change in arterial or coronary venous 2,3-diphosphoglycerate in an isolated supported canine heart preparation after intracoronary administration of OISB. Litwin et al[10] found significantly increased P_{50} values in dogs after a single intravenous infusion of 400 mg/kg of OISB which was sustained for 7 days in intact animals.

In the isolated heart model there is convincing evidence of a physiologically significant effect of reduction of blood oxygen affinity by OISB: during rapid atrial pacing (190 or 230 beats/min) and maintenance of constant left ventricular systolic pressure and coronary blood flow, intracoronary OISB infusion resulted in significant increases in coronary venous P_{50}, myocardial oxygen consumption, and oxygen extraction without change in coronary venous or arterial pO_2; that is, as myocardial oxygen demand was increased by tachycardia, OISB apparently enhanced oxygen release from hemoglobin and improved oxygen utilization by the myocardium while coronary venous pO_2 remained constant, thus providing an unchanged oxygen diffusion gradient across the myocardium.[11] OISB also reduced heart rate and left ventricular systolic pressure, resulting in diminished myocardial oxygen consumption and oxygen extraction as well as *increased* coronary venous pO_2 in this nonischemic isolated heart preparation.[11]

During global ischemia in the isolated canine heart (with heart rate maintained constant at 150 beats/min by atrial pacing), intracoronary OISB infusion produced significant increases in coronary venous pO_2: thus ischemic myocardium extracted more oxygen from its reduced blood supply after OISB treatment. Perhaps even more importantly, OISB treatment produced significant increases in myocardial contractile force, left ventricular systolic pressure, and LV dP/dt, suggesting OISB-related improvement in the *function* of ischemic myocardium.[11]

Because these studies suggested that OISB acts both to increase the extraction of oxygen from blood perfusing the coronary arteries and to reduce heart rate, we reasoned that this agent might have beneficial effects on the regionally ischemic heart, by effecting an increase in myocardial oxygen supply or a decrease in myocardial oxygen demands, or both. Our pilot studies (Protocol I) confirmed that this intervention, similar to others known to protect ischemic myocardium,[1–3] reduced epicardial S-T segment elevation over the ischemic zone after transient LAD coronary artery occlusions. Reduction in epicardial S-T segment elevation is thought to reflect, in a directional sense, an amelioration of myocardial ischemic injury.[1,12] To define more quantitatively the effects of OISB on the ischemic process, we performed further experiments (Protocol II) which demonstrated that administration of OISB before permanent coronary occlusion was associated with less myocardial necrosis than observed in a control group of animals with similarly placed coronary artery ligations. Randomization procedures and investigator blinding were used to eliminate sources of bias in this part of our study, and the variability in infarct size after LAD occlusion was minimized by prerandomization

exclusion of animals which did not develop cyanosis of both the anterior wall and cardiac apex during a test coronary ligation. Protocol III experiments then confirmed that OISB effected a reduction in acute ischemic injury, even when its administration was begun *after* coronary occlusion. Furthermore, OISB reduced heart rate and left ventricular contractility when it was administered after coronary occlusion (Protocol III); such changes in major determinants of myocardial oxygen consumption may have reduced myocardial oxygen demand, leading to less oxygen lack in the ischemic zone. It is not clear from our studies whether these hemodynamic alterations are physiologic concomitants of improved oxygen extraction by peripheral tissues[22] or whether they reflect a direct cardiodepressant effect of OISB. The absence of changes in either central ischemic zone or summed transmural ischemic zone regional myocardial blood flows after OISB therapy indicates that the protective effect of this intervention is not due to an increase in the volume of blood flow to ischemic tissue. These findings are compatible with the hypothesis that a decrease in blood oxygen affinity, confirmed by the increase in P_{50} after OISB infusion in a subpopulation of our study animals, allows more extraction of oxygen from available collateral blood flow, thus improving oxygenation in ischemic myocardium. Further studies will be necessary to delineate whether the negative inotropic and chronotropic effects of OISB play a major or only a supportive role in the reduction of ischemia by OISB.

Another group recently demonstrated salutary effects of reduced blood oxygen affinity on regional ischemic injury after coronary artery occlusion.[23] In these studies, infusion of a solution of glycolytic intermediates (dihydroxyacetone, phosphate, and pyruvate) produced an increase in blood P_{50} similar in magnitude to that observed in our studies with OISB; when ischemic tissue was classified according to the degree of regional blood flow reduction, dogs with reduced blood oxygen affinity had less histologic evidence of necrosis for any degree of ischemia than either control dogs or those receiving equivalent volumes of pyruvate and phosphate. The intervention tested in these studies is known to stimulate production of 2,3-disphosphoglycerate[24]; this mechanism of blood oxygen affinity reduction is different from that of OISB.[11]

We conclude that acute myocardial ischemic injury (assessed by epicardial electrocardiographic S-T segment mapping) and ultimate infarct size are reduced in dogs by infusion of o-iodo sodium benzoate before coronary artery occlusion. Furthermore, OISB infusion after the onset of coronary occlusion also reduces acute myocardial ischemic injury in anesthetized dogs. Further studies will be required to delineate more precisely the mechanism of myocardial protection by OISB and the role of it and other drugs which reduce blood oxygen affinity in efforts to ameliorate myocardial damage resulting from acute and chronic myocardial ischemia.

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Relation of Immediate and Delayed Thallium-201 Distribution to Localization of Iodine-125 Antimyosin Antibody in Acute Experimental Myocardial Infarction

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Thallium-201 (Tl-201) distribution in acute experimental myocardial infarction (MI) (n = 18) was compared with cardiac-specific antimyosin Fab (AM-Fab) uptake, a specific marker for myocardial necrosis. When antimyosin was injected 4 hours after ligation with Tl-201 administered 23 hours 55 minutes later and measurement of myocardial distribution determined 5 minutes after intravenous administration of Tl-201, (1) Tl-201 distribution closely correlated with microsphere regional blood flow, and (2) an inverse exponential relation to iodine-125 (I-125) AM-Fab uptake was apparent. In another group of 4 animals, Tl-201 and AM-Fab were administered intravenously 4 hours after MI, and 36 hours later myocardial distribution was measured. This delayed Tl-201 distribution had a close inverse linear correlation with I-125 AM-Fab uptake. This inverse linear relation also was apparent in 28-hour-old MIs in dogs (n = 4) where collateral circulation had been established. Tl-201 was administered intravenously at 27 hours after MI, and Tl-201 distribution was determined 1 hour later. The present study demonstrated that whereas immediate Tl-201 distribution is flow-limited, delayed Tl-201 distribution is a marker of cell viability which, due to prolonged circulation time and redistribution, is not flow-limited.

Therapy to restore coronary blood flow in patients with acute myocardial infarction (MI) has been evaluated both by return of myocardial perfusion, demonstrated with thallium imaging, and the restoration of ventricular function. Since thallium-201 (Tl-201) uptake is believed to occur exclusively in nonnecrotic tissues[1,2] and early thallium uptake is linearly related to blood flow,[3–5] thallium imaging may provide the most suitable marker for acute improvement. Yasuda et al[6] demonstrated a lag in the return of function in several patients successfully treated with intracoronary streptokinase. The factors controlling the delayed distribution of thallium, however, are not as well defined. Studies by Pohost,[4] Beller,[7] and co-workers suggest that the concentration of Tl-201 in ischemic myocardium 2 to 3 hours after intravenous injection is not related to flow. It has been postulated that the late distribution of Tl-201 in myocardium is related to viable cell mass. Cardiac myosin-specific antibodies labeled with iodine-125 (I-125) localize in necrotic myocytes[8] and thus are highly specific markers for MI.[9–11] Studies were performed in experimental animals with acute coronary occlusion to compare the distribution of radiolabeled antimyosin antibody with immediate and delayed distribution of Tl-201.

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Methods

Preparation of cardiac-specific antimyosin Fab (AM-Fab): Purification of canine cardiac myosin was by the method of Katz et al[12] as described previously.[9–11] Antisera were prepared in New Zealand White rabbits, and antibody specific for cardiac myosin was purified by affinity chromatography with canine cardiac myosin-Sepharose immunoadsorbent.[9] Anticardiac myosin Fab (AM-Fab) were prepared by papain digestion of purified whole antibody at 37°C for 1.5 hours at pH 7.0 by the method of Porter.[13] Fab were separated from crystallizable fragment (Fc) and undigested antibody

by chromatography on a protein-Sepharose immunoadsorbent.[14] (Protein-A binds Fc and undigested whole IgG but does not bind Fab.) AM-Fab thus obtained were concentrated by vacuum dialysis then dialyzed against 0.3 M phosphate-buffered saline solution, pH 7.0.

Antibody activity of AM-Fab was tested by degree of binding to I-125 canine cardiac myosin. AM-Fab were iodinated with I-125 by the lactoperoxidase procedure of Marchalonis.[15] I-125 (10 mCi) was used to iodinate 250 μg AM-Fab with a resultant 50 to 60% radioiodine incorporation at an enzyme to substrate ratio of 1:50. The radiolabeled AM-Fab were repurified utilizing a 10-ml myosin-Sepharose column. Active I-125-AM-Fab were desorbed from the immunoadsorbent with 5 *M* guanidine-hydrochloride and renatured by sequential dialysis with an excess of 3 *M* potassium chloride, then against phosphate-buffered saline solution. Approximately 1 to 1.5 mCi of repurified I-125-AM-Fab was obtained from each iodination for this study.

Experimental MI: Eighteen mongrel dogs were anesthetized with 30 mg/kg of pentobarbitol, intubated, and placed on a Harvard pump respirator. A thoracotomy was performed on each dog at the fourth intercostal space and the heart suspended in a pericardial cradle.[9,16] The left anterior descending coronary artery (LAD) was dissected free at approximately two-thirds the distance from apex to base and occluded with a silk ligature. This ligation usually affected approximately 30% of the left ventricular myocardium as determined by the extent of cyanosis. The thoracotomy was closed, and the animals were allowed to recover.

Experimental protocol: Three different experimental protocols (I to III) were employed to study the relation of Tl-201 distribution to viable myocardial cell mass. Each protocol was performed in 6 dogs; however, 2 dogs each from Groups I and III and 3 from Group II were lost due to ventricular fibrillation after LAD occlusion. Figure 1 is a schematic diagram of the 3 protocols. The LAD was occluded in all dogs as described previously. At 4 hours after LAD occlusion, 200 μCi of I-125-AM-Fab was administered intravenously.

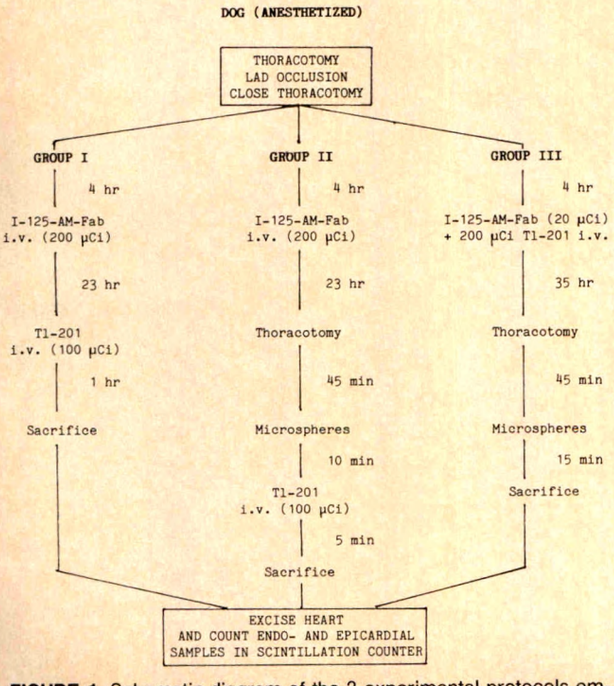

FIGURE 1. Schematic diagram of the 3 experimental protocols employed to study Tl-201 distribution with respect to viable myocardial mass as determined by cell death criteria of AM-Fab localization. i.v. = intravenously.

In Group I, each of the 4 living dogs received 100 μCi Tl-201 by intravenous injection 23 hours after administration of the I-125-AM-Fab. One hour later, the animals were killed by pentobarbitol overdose. The hearts were excised immediately and cut into 1 cm-thick ventricular slices parallel to the atrioventricular groove. Each ventricular slice was cut into 8 to 10 equal pieces and then further subdivided into epicardial and endocardial samples. All tissue samples were counted in an automatic scintillation gamma counter (Packard) for relative distribution of Tl-201 and I-125 activities. Windows were set at 80 to 200 keV for Tl-201 counting and 15 to 50 keV for I-125 activity. Corrections were made for Tl-201 activity in the iodine window. Normal epicardial and endocardial samples (4 each) obtained from the posterior left ventricular myocardium were used for comparison with the rest of the myocardial samples for distribution of various radioisotopes.

In Group II, the 3 living dogs were reanesthetized 23 hours after intravenous administration of the I-125-AM-Fab, and the thoracotomy was reopened. Forty-five minutes later, a bolus of 3×10^6 scandium-46 (Sc-46) carbonized microspheres (8 to 10 μm, 3M, St. Paul, Minnesota) was injected into the left atrium for determination of relative regional blood flow. Ten minutes after microsphere injection, 100 μCi of Tl-201 were administered by intravenous injection, and the animals were killed exactly 5 minutes later by pentobarbitol overdose. Relative distribution of I-125, Tl-201, and Sc-46 activities in the various samples of the myocardium was determined as described for Group I with an additional window of 680 to 1,000 keV for Sc-46 activity.

The 4 living dogs in Group III were given 200 μCi of I-125-AM-Fab and 200 μCi of Tl-201 intravenously simultaneously at 4 hours of LAD occlusion. Thirty-six hours later, the animals were killed. Fifteen minutes before death, a bolus of 3×10^6 Sc-46 microspheres was injected into the left atrium as previously described. The hearts were excised, and distribution of I-125, Tl-201, and Sc-46 activities in the myocardial samples was determined as described for Groups I and II.

Comparison of Tl-201 with regional blood flow: Data obtained from Groups II and III were reanalyzed for comparison of Tl-201 distribution at 5 minutes and 36 hours after intravenous injection of Tl-201 to the corresponding regional myocardial blood flow. Computer curve fitting was performed as described later.

Statistical analyses: At least 4 endocardial and 4 epicardial samples from the posterior left ventricular myocardium of each animal were employed as controls to determine mean uptake and distribution of I-125-AM-Fab and Tl-201. In studies involving comparison of relative antibody uptake to thallium distribution or relative regional blood flow, best-fit linear regression curves relating antibody uptake to Tl-201 or flow were determined by utilizing the formula $y = a + bx$, where y = log (percent blood flow) or log (percent Tl-201) and x = relative antibody uptake; or, in case of inverse relations, y = percent blood flow or percent Tl-201 and x = antibody uptake. Constants *a* and *b* were obtained by the method of Snedecor and Cochran.[17]

Results

The relation of I-125-AM-Fab localization to 1 hour of Tl-201 distribution determined at 28 hours after LAD occlusion is demonstrated in Figure 2. There is an in-

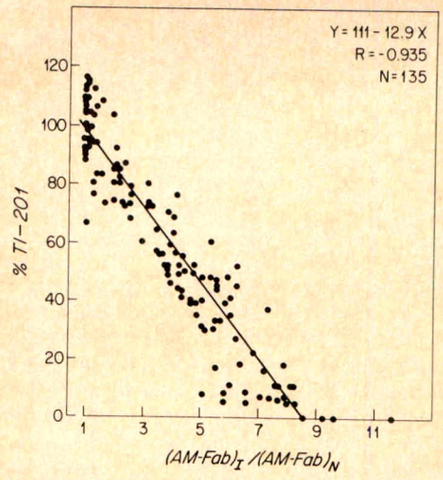

FIGURE 2. Relation between AM-Fab uptake and Tl-201 distribution in 28-hour-old experimental MI: y = 111 − 12.9x, where y = percent flow and x = (AM-Fab)I/(AM-Fab)N.

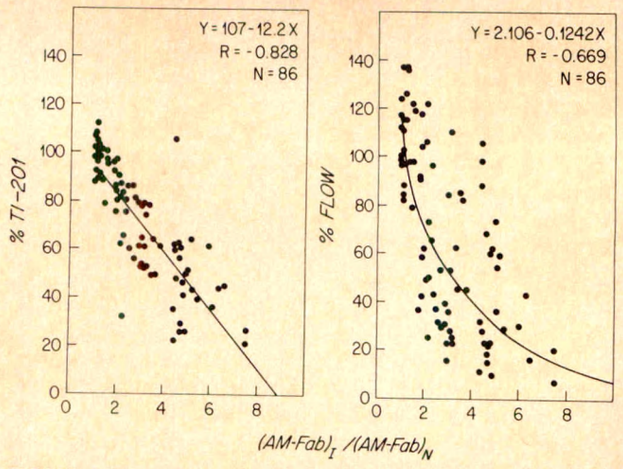

FIGURE 4. Simultaneous comparison of AM-Fab uptake and Tl-201 distribution and regional myocardial blood flow. **Left,** relation between antibody uptake and Tl-201 distribution 36 hours after antibody and Tl-201 intravenous injection. **Right,** relation between antibody uptake and regional myocardial blood flow.

verse relation between Tl-201 distribution and AM-Fab uptake. In the region of normal myocardium, determined by lack of an antibody uptake ratio above 2 (1.15 ± 0.18, mean ± standard deviation [SD]), Tl-201 distribution was 100 ± 11.2% of average normal posterior left ventricular myocardial Tl-201 distribution. Only 1 sample point showed Tl-201 distribution at 67%. The correlation coefficient was highly significant at −0.935 ($p < 0.001$). This contrasted with the Tl-201 distribution of 5 minutes (determined by injection at 27 hours 55 minutes after LAD occlusion and sacrifice of the animal 5 minutes later) compared with AM-Fab uptake at 28 hours of LAD occlusion (Fig. 3, left panel). The relations between AM-Fab uptake and blood flow and between AM-Fab uptake and Tl-201 distribution (5 minutes) were not significantly different ($r = -0.856$ and -0.85, respectively; $p > 0.5$) (Fig. 3). In regions of normal myocardium showing AM-Fab uptake of less than a ratio of 2 (1.22 ± 0.3, mean ± SD), mean regional blood flow was 88.4 ± 20.2% and mean Tl-201 distribution was 92 ± 16.9% (p = not significant [NS]).

When AM-Fab uptake at 36 hours of antibody circulation was compared with Tl-201 uptake and regional blood flow, Tl-201 distribution was inversely proportional to AM-Fab uptake ($r = -0.828$), whereas regional blood flow still showed an inverse exponential relation ($r = -0.669$, $p < 0.001$) (Fig. 4). In this delayed Tl-201 distribution study, regions of normal myocardium determined as regions with AM-Fab uptake of less than a ratio of 2 (1.34 ± 0.3) showed mean Tl-201 distribution of 95.3 ± 8.6%, whereas mean percent flow in the same samples was 101.3 ± 25.

Figure 5 demonstrates the comparison of Tl-201

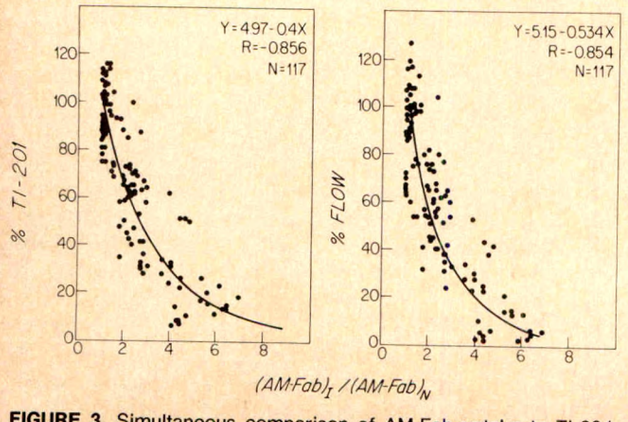

FIGURE 3. Simultaneous comparison of AM-Fab uptake to Tl-201 distribution and regional myocardial blood flow at 5 minutes of Tl-201 distribution in 28-hour-old experimental MI.

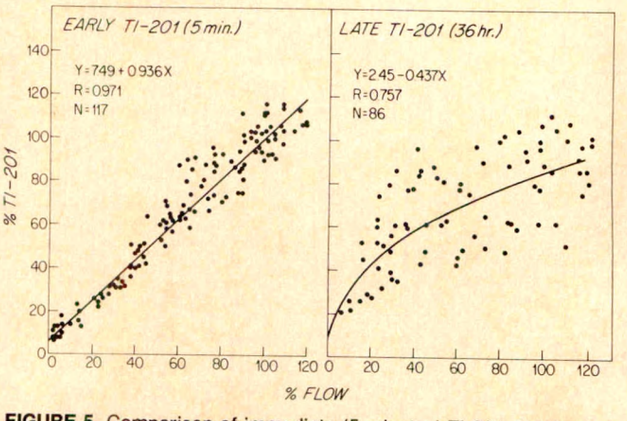

FIGURE 5. Comparison of immediate (5 minutes) Tl-201 distribution to regional myocardial blood flow at (**left**) 28 hours of coronary occlusion: y = a + bx, where y = percent Tl-201, x = percent flow, a = 7.49, b = 0.936, and $r = 0.971$, and (**right**) 36 hours of Tl-201 distribution to regional myocardial blood flows in 40-hour-old experimental myocardial infarcts: y = a + bx, where y = 1n percent Tl-201, x = percent 1n flow, a = 2.45, b = 0.437, and $r = 0.757$.

distribution to regional blood flow for 28- and 40-hour-old infarcts with Tl-201 distribution determined at 5 minutes and 36 hours of circulation. As expected, 5-minute Tl-201 distribution is reflective of regional blood flow demonstrating a direct proportionality (r = +0.971). While 36-hour distribution is diphasic, with near normal Tl-201 uptake in tissue samples in which regional flow has been reduced to 40% of normal, a more drastic reduction of Tl-201 uptake is noted in regions of hypoperfused myocardium (r = 0.757).

Discussion

We have demonstrated with primary neonatal murine myocytes in culture that antimyosin bound covalently to 1 μm polystyrene beads binds only to necrotic myocytes.[18,19] This observation was confirmed by fluorescence-activated cell sorting as well as by scanning electron microscopy. We have also previously demonstrated that antimyosin is highly specific for myocardial necrosis by macro- and microautoradiography, and by histochemical and histologic criteria.[8] Based on these studies, where antimyosin localization occurs only in necrotic myocytes, we have now used antimyosin uptake as a standard for determination of cell necrosis for comparison with Tl-201 distribution.

Tl-201 imaging, with injection either at rest or during exercise, has been used in clinical studies to identify ischemic or infarcted regions of myocardium.[1–4,7] Although many studies support the concept that the initial distribution of thallium is a linear function of blood flow,[3,4] at most clinically relevant blood flows, the factors controlling the redistribution of thallium have not been well defined. Recent studies[4,20–22] suggest that redistribution is independent of blood flow. This study suggests that the distribution of Tl-201 several hours after administration in acute MI and labeled antimyosin localization are inversely proportional. These data support the contention that delayed thallium scans represent the distribution of viable myocardium (r = −0.935 and −0.828). There appears to be little difference between 1 hour and 36 hours of thallium distribution in this relation (slopes −12.35 and −12.27, $p > 0.5$), suggesting that in an older MI where collateral circulation has already been established, serial distribution need not continue beyond 1 hour to allow evaluation of viability at least in experimental animals. However, in fresh MIs, 2 hours of Tl-201 redistribution may be required for evaluation of cell viability as observed by Pohost et al.[4]. This difference in time may be due to the difference in the amount of collateral circulation. Immediate thallium distribution (at 5 minutes), on the other hand, results in a very different slope in relation to antibody uptake (−17.9, $p < 0.01$). This relation is not significantly different from the relation between antibody uptake and flow (slope = −18.5), indicating that determination of thallium distribution 5 minutes after intravenous administration is directly proportional to regional blood flow (Fig. 5), which is in agreement with reported data.[4] DiCola et al,[23] employing a 24-hour-old canine infarct model, also showed flow dependence of thallium distribution when thallium was injected shortly before the animal was killed.

Thus, at 1 hour or 36 hours after thallium injection, the distribution of radionuclide is not limited by regional blood flow in older infarcts, but appears to reflect cell viability. We have previously demonstrated that antimyosin antibodies localize specifically in infarcted myocardium over and above the extent of nonspecific adsorption of control IgG.[9–11] This specificity has also been demonstrated by microautoradiography[8] where only necrotic myocytes showed antimyosin localization, whereas normal myocardium did not show antimyosin adsorption. These studies indicated that antimyosin localizes only in necrotic cells. By this criterion of cell necrosis, mean thallium uptake in normal myocardium was 95.3 ± 8.6%, whereas average flow in these same samples was 101.3 ± 25% (Fig. 4). A possible explanation of the observed gradient of increasing antibody uptake and decreasing thallium uptake from normal tissue to the center of an infarcted region may well be related to a varying admixture of viable and necrotic cells. Near the periphery of the ischemic zone where the cells are largely viable, thallium is taken up, with some antibody uptake in a small number of necrotic cells. As one proceeds to the center of the infarct, there are more necrotic cells that take up antibody and fewer viable cells that take up thallium. If, however, ischemic cells take up thallium at a reduced concentration, then the cells in the periphery of the ischemic zone would show reduced thallium uptake, and since these are still viable cells, the antibody uptake would remain at about a ratio of 1. If such were the case, the relation between delayed thallium and antimyosin uptake would be similar to that of percent flow and antimyosin uptake. However, the data indicate an inverse linear relation between delayed thallium uptake and antimyosin localization, indicating that the region of MI is a mixture of viable and necrotic myocytes with maximum necrotic myocytes at the center of the MI.

In immediate (5 minutes) thallium distribution, which appears to be flow-limited, there may be regions of viable cells that take up neither thallium nor antibody. Antibody is not taken up because it is excluded by intact cell membranes. Thallium is not taken up because there has been insufficient time for adequate concentration of this radionuclide to reach cells which have the potential of adequate uptake.

The data presented in our report demonstrating delayed thallium distribution as an indicator of myocardial cell viability may be of importance in view of the recent studies utilizing intracoronary streptokinase, angioplasty, or both to recanalize occluded coronary vessels.[24–26] These invasive interventions are aimed at salvaging jeopardized myocardium. Intravenous thallium distribution images obtained before recanalization provided images of the areas at risk, whereas thallium images obtained after recanalization should provide images including areas of viable myocardium in the jeopardized zones salvaged by the intervention. The differences between the pre- and postrecanalization thallium images should provide areas of salvaged myocardium. Return of cardiac function after recanalization has not been observed to be a sensitive parameter for determination of myocardial salvage.[6] Whether Tl-201 images obtained immediately after

recanalization with a second dose of intravenous thallium would provide information regarding the salvaged myocardium is not clear; however, a delayed image after recanalization should provide areas of thallium uptake in viable myocardium. Comparison of pre- and postrecanalization thallium images should thus provide scintigraphic data demonstrating the outcome of the intervention.

In conclusion, this study has demonstrated that (1) late thallium distribution reflects cell viability rather than regional blood flow; (2) immediate thallium distribution at 5 minutes of circulation is an indicator of relative blood flow, the analysis of which may significantly overestimate the area of irreversibly damaged myocardium; and (3) the comparison of immediate and delayed Tl-201 images could provide information concerning the zone of reversible ischemic compromise.

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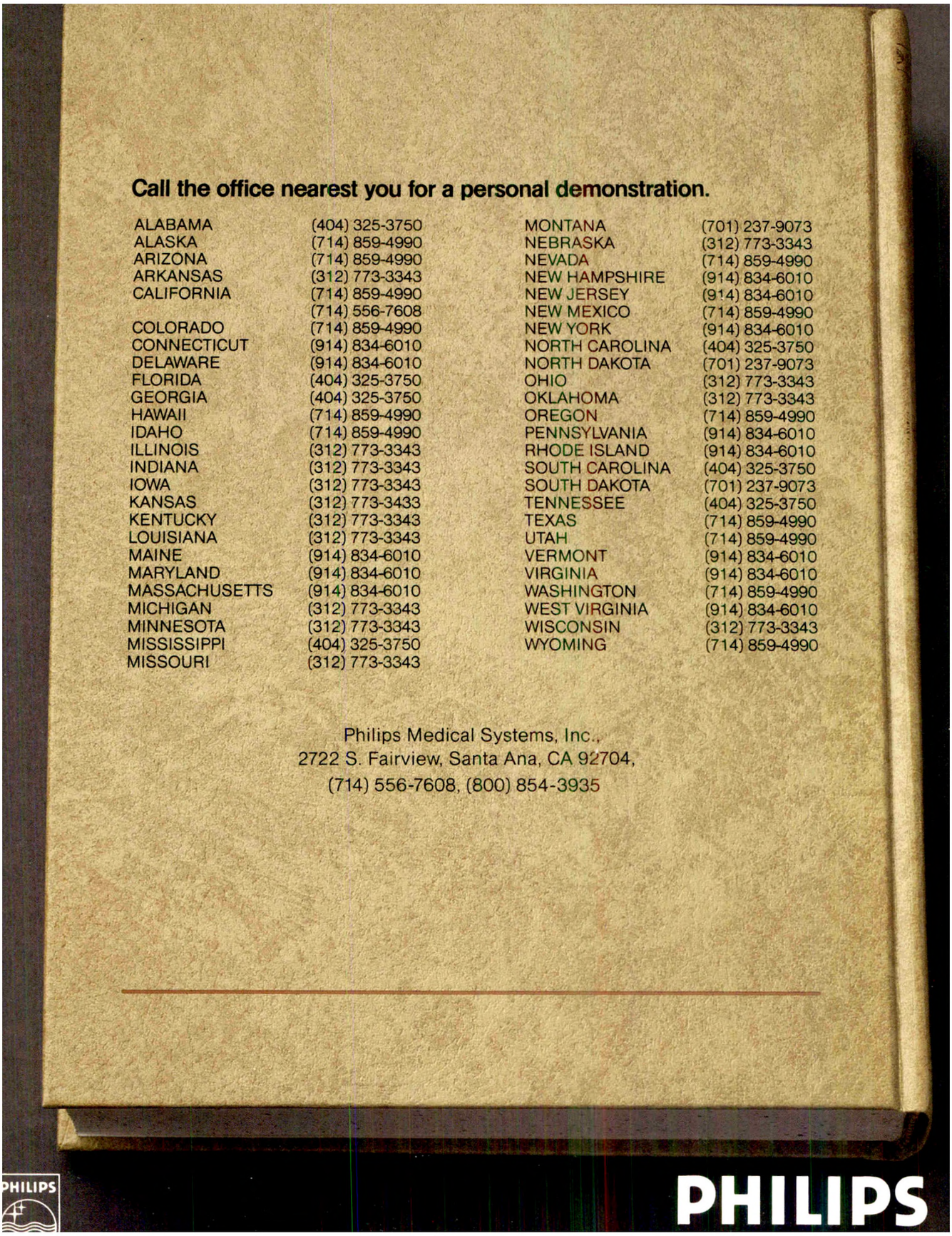

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Nature of "Residual Fast Channel" Dependent Action Potentials and Slow Conduction in Guinea Pig Ventricular Muscle and Its Modification by Isoproterenol

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The nature of "residual fast channel" dependent action potentials and conduction was studied in guinea pig ventricular papillary muscle in which the resting potential was reduced to 58 ± 1 mV in high K^+ (16.7 m*M*) Tyrode's solution, with or without isoproterenol (0.1 μM). In the absence of isoproterenol, the action potential had a slur on the upstroke and the maximum rate of rise ($\dot{V}_{max}$) was composed of 2 separable peaks: the early large (32 ± 7 V/s, $\dot{V}_{max,fast}$) and the late small (10 ± 2 V/s, $\dot{V}_{max,slow}$) ones. The conduction velocity ranged from 30 to 35 cm/s. The $\dot{V}_{max,fast}$ was selectively depressed by tetrodotoxin (1 μM) and the $\dot{V}_{max,slow}$, by l-verapamil (1 μg/ml), indicating that the impulses were transmitted through incompletely inactivated ("residual") fast channels. Lidocaine (2 μg/ml) depressed $\dot{V}_{max,fast}$ with reduction of conduction velocity to about 20 cm/s just before the conduction block. Isoproterenol quadrupled the $\dot{V}_{max,slow}$ but decreased $\dot{V}_{max,fast}$. As a result, the $\dot{V}_{max,slow}$ overrode the $\dot{V}_{max,fast}$ without change in the conduction velocity. In the absence of isoproterenol, there was no rate-dependent change in the action potential duration and the effective refractory period among the rates of 0.1, 0.5, and 0.9 Hz. Isoproterenol produced rate-dependent shortening in action potential duration with rate-independent shortening of postexcitation refractoriness, thereby resulting in a significant shortening in the effective refractory period at faster rates (0.5 and 0.9 Hz). Results suggest that the "residual fast channel" could produce "slow conduction" and that the ionic channels (fast or slow) responsible for the slow conduction may alternate according to local concentrations of tissue catecholamines.

During the acute phase of myocardial ischemia, there is a rapid increase in extracellular potassium ion (K^+) concentration up to about 16 m*M* in the ischemic zone during the first 10 to 20 minutes of coronary artery occlusion in in vivo animals.[1–4] In addition, there is evidence that norepinephrine is released immediately after myocardial anoxia[5] or ischemia[6–8] from the sympathetic nerve terminals.

These conditions (hyperkalemia and catecholamines), in combination with acidosis, appear to be the most important factors responsible for arrhythmias during the early phase of ischemia because such changes should predispose to initiation of the slow response which are prerequisite for the development of reentry.[9] In fact, some ventricular arrhythmias have been successfully treated by slow channel blockers such as verapamil[10] and diltiazem.[11,12] On the other hand, there is much clinical evidence that many ventricular tachyarrhythmias related to myocardial infarction can be treated with lidocaine, which blocks the fast sodium channel without effects on the slow channel.[13] Thus uncertainties remain as to the ionic mechanism of reentry and the effectiveness of lidocaine in ventricular arrhythmias in acute myocardial infarction.[14–16] For this reason, we carried out the present experiments to clarify (1) the ionic channel or channels responsible for the impulse generation and conduction in the very early phase of acute myocardial ischemia, (2) the modification of the impulse generation and conduction by catecholamine (isoproterenol), and (3) the mode of action of antiarrhythmic drugs (lidocaine and verapamil) on such a response.

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Methods

Guinea pigs weighing 250 to 300 g were killed by a blow on the neck. The heart was quickly removed and the papillary muscles (5 to 8 mm long and 0.8 to 1 mm in diameter) were excised from the right ventricle. The tendinous end of the preparation was pinned on the rubber floor of a 0.9 ml muscle chamber and the other end was fixed by a ring-shaped silver-silver chloride wire (ring electrode) wrapped 1 mm proximal to the end. Rectangular pulses of 3 ms duration were applied between the ring electrode and the small (3 by 3 mm) platinum plate was attached to the cut end of the preparation. The muscle was usually stimulated at a rate of 0.1 Hz but in some experiments at more rapid rates (0.5 to 0.9 Hz). Only cathodal pulses of constant intensity (1.5 to 2.0 times the threshold strength) were used for the stimulation because, in preliminary experiments, anodal pulses of different intensity often affected the amplitude of the maximum rate of rise ($\dot{V}_{max}$) of action potentials. Change in stimulus intensity within the range slightly changed the intervals between stimulus artifact and the action potential upstroke, but without change in the $\dot{V}_{max}$.

The muscle was perfused with normal or K^+-enriched Tyrode's solution with or without drugs. The composition of normal Tyrode's solution in mmol/liter was as follows: NaCl 137, KCl 5.4, $MgCl_2$ 1.0, $CaCl_2$ 1.8, $NaHCO_3$ 12, $NaHPO_4$ 0.4, and glucose 5.0. The high K^+ (16.7 m*M*)-Tyrode's solution was prepared by adding appropriate amounts of KCl to the normal Tyrode's solution without adjusting the osmolarity. We chose 16.7 m*M* K^+ concentration for 2 reasons: (1) extracellular K^+ concentration was reported to increase up to this level at the center of the ischemic zone in experimental myocardial infarction[2,3]; (2) preliminary experiments revealed that the split $\dot{V}_{max}$ described later (see Fig. 1) could be recognized at K^+ concentrations of 14 to 18 m*M*; and (3) K^+ concentrations over these levels (for example, 20 m*M*) resulted in inexcitable preparations in the absence of catecholamine.

In some experiments, high K^+ Tyrode's solution containing the following drugs was used: isoproterenol (Nakarai), lidocaine (Fujisawa), l-verapamil (Knoll), and tetrodotoxin (Sankyo).

The membrane potential was measured with conventional glass microelectrodes filled with 3 mol KCl (resistance, 10 to 30 MΩ). The action potentials were differentiated with an electronic differentiator having a linear amplification rate of 0 to 500 V/s. To measure the conduction velocity, 2 microelectrodes were impaled along the same line on the longitudinal axis of the preparation at a distance of 1.6 to 2.5 mm. The differentiated signals were led either to different channels (Fig. 1A) or to the same channel (Fig. 1B). The former was used to measure the amplitude of the $\dot{V}_{max}$ of each action potential, while the latter served as a feasible measure of the conduction time which was determined as the interval between 2 prominent peaks (Fig. 1B, bottom tracing). The (apparent) conduction velocity was calculated by dividing the distance between the 2 microelectrode tips by the conduction time. The signals were monitored on an oscilloscope (Nihonkoden VC-9) and recorded by a long recording camera (Nihonkoden RLG-6101).

After about 1 hour of equilibration in normal Tyrode's solution gassed with 95% oxygen-5% carbon dioxide, the muscle was initially perfused with high K^+ Tyrode's solution without the drugs followed by perfusion with the drug-containing solutions. Transitional and steady-state effects were recorded during the actions of each drug and data compared with control findings. The pH of all solutions was 7.3 and the temperature was kept at 35.0 ± 0.2°C with a constant flow rate of 3.0 ml/min.

Statistical evaluation of the results was made with Student's *t* test, and p values <0.05 were considered significant. The experiments were performed in 49 papillary muscles obtained from 40 guinea pig hearts. Nineteen preparations were used for preliminary experiments to establish the method of stimulation and to determine the external K^+ concentration which appeared pertinent to produce split $\dot{V}_{max}$. Twenty preparations were used for the experiments on depolarization phase (Fig. 1 to 7) and the rest of the preparations for the experiments on repolarization phase (Fig. 8 and 9). Only the

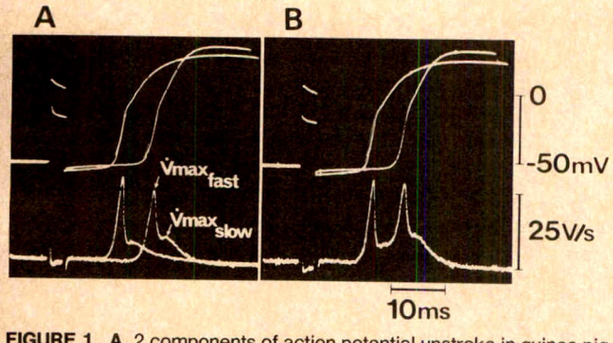

FIGURE 1. A, 2 components of action potential upstroke in guinea pig ventricular papillary muscle perfused in 16.7 m*M* K^+ Tyrode's solution and stimulated at 0.1 Hz. **Upper tracings,** action potential upstrokes obtained from 2 microelectrodes impaled 1.9 mm apart along the preparation; **lower tracings,** first derivatives of each action potential. Note initial rapid and later slow rising phase in each action potential tracing (**top**) associated with double-peaked appearance of the differentiated tracing (**bottom**), as indicated by **arrows** ($\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$). **B,** same penetration as in panel A except that here the differentiated signals were coupled to the same input of the oscilloscope to measure conduction time as a distance between the 2 peaks of the $\dot{V}_{max}$ tracing. Interelectrode distance (1.9 mm) and conduction time (6.0 ms) gave a conduction velocity of 0.32 m/s in this preparation.

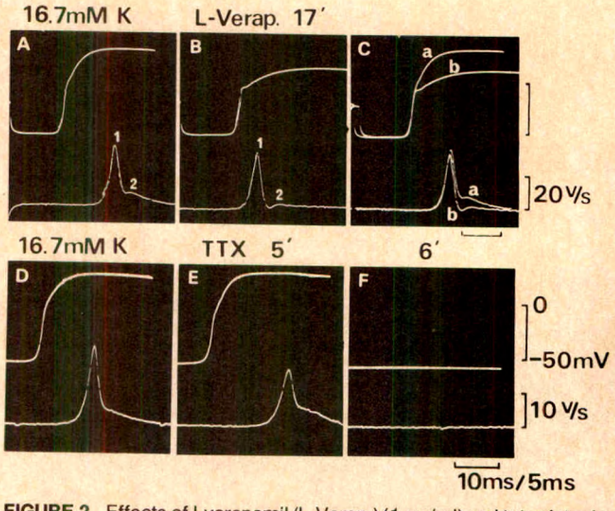

FIGURE 2. Effects of l-verapamil (L-Verap.) (1 μg/ml) and tetrodotoxin (TTX) (1 μ*M*) on the upstroke phase and $\dot{V}_{max}$ of the action potential in 16.7 m*M* K^+ Tyrode's solution. **A,** control. **B,** 17 minutes after l-verapamil. **C,** superposition of A and B. Numerals 1 and 2 denote $\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$, respectively, as indicated in Figure 1A. Note the selective decrease in $\dot{V}_{max,slow}$ with little change in $\dot{V}_{max,fast}$ by l-verapamil. **D,** control (different preparation). **E and F,** 5 and 6 minutes after application of tetrodotoxin. Note the selective decrease in $\dot{V}_{max,fast}$ (**E**) followed by complete loss of excitability (**F**).

data obtained during a continuous impalement were accepted for analysis in each experimental procedure, and the other experiments were used to support the results.

Results

Ionic mechanism of the upstroke phase in high K^+ media: An increase of K^+ in the perfusing media from normal (5.4 m*M*) to high concentration (16.7 m*M*) led to a depolarization in the resting membrane potential and depressed the action potential upstroke, as is known.[9] Figure 1A shows the high K^+-induced change in the upstroke and corresponding first derivative in action potentials recorded from 2 different points along the same preparation. The impulse was conducted from the left-hand action potential to the right.

In normal K^+ concentration, the average resting potential was -84.9 ± 4.9 mV (n = 9) and the upstroke phase consisted of a single-peaked, rapid component with a maximum upstroke velocity ($\dot{V}_{max}$) of 164.9 ± 14.0 V/s (not shown). With increase in the K^+ concentration, the upstroke changed the configuration which consisted of 2 distinct phases, as depicted by arrows in Figure 1A: an early rapid component ($\dot{V}_{max,fast}$) followed by a slow component ($\dot{V}_{max,slow}$) and resulting in a double-peaked $\dot{V}_{max}$ (split $\dot{V}_{max}$). In about 20% of the preparations tested, however, the $\dot{V}_{max,slow}$ declined rather monotonously with no discernible peak (compare with Fig. 2D, bottom tracing). In such cases, we used a point of inflection from rapid decay of the $\dot{V}_{max,fast}$ to slow decay of the $\dot{V}_{max,slow}$ to determine the amplitude of the $\dot{V}_{max,slow}$.

The average resting potential measured from 6 preparations in the high K^+ media (16.7 m*M*) was -58 ± 1 mV (range -57 to -60 mV), while the amplitude of $\dot{V}_{max,fast}$ was 32 ± 7 V/s and that of $\dot{V}_{max,slow}$, 10 ± 2 V/s.

To elucidate possible ionic channels contributing to the different upstroke phases, we used l-verapamil and tetrodotoxin, as the former blocks slow channels[17,18] and the latter blocks fast channels.[9,19]

Figure 2A to C shows the effect of l-verapamil (1 μg/ml) on the upstroke phase in the K-enriched media. The drug depressed only the late slow component with no change in the early fast component of the upstroke and resulted in a marked decrease in $\dot{V}_{max,slow}$ with little change in $\dot{V}_{max,fast}$ (Fig. 2C). The excitation was not abolished even after a prolonged application of over 30 minutes. On the other hand, Figure 2D to F represents the effect of tetrodotoxin (1 μM), which selectively depressed the early rapid upstroke, was associated with a marked decrease in $\dot{V}_{max,fast}$ (Fig. 2E), and was followed by a complete loss of excitability (Fig. 2F).

These findings suggested that in the ventricular muscle depolarized by high extracellular K^+ concentration to these potential levels, the action potential upstroke consisted of both fast and slow channels, and that the fast channel, even though it is all but inactivated by depolarization, still plays an essential role in the generation of impulse and conduction. Thus we will hereafter term the conduction "residual fast channel-dependent slow conduction."

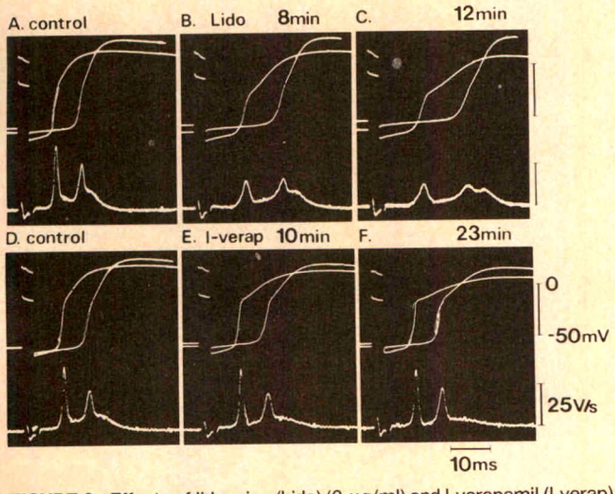

FIGURE 3. Effects of lidocaine (Lido) (2 μg/ml) and l-verapamil (l-verap) (1 μg/ml) on action potential upstroke and impulse conduction in 16.7 m*M* K^+ Tyrode's solution. **A,** control. **B and C,** 8 and 12 minutes after application of lidocaine. **D,** same preparation (30 minutes after washout of the lidocaine effects in panel C). **E and F,** 10 and 23 minutes after application of l-verapamil. Note that lidocaine decreased $\dot{V}_{max,fast}$ and lengthened conduction time (**B and C**) while l-verapamil had no effect on $\dot{V}_{max,fast}$ or conduction time but did depress $\dot{V}_{max,slow}$ (**E and F**).

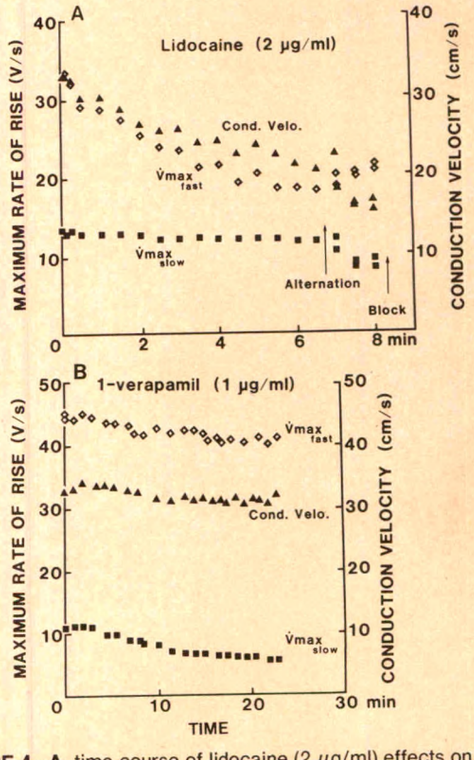

FIGURE 4. **A,** time course of lidocaine (2 μg/ml) effects on the amplitude of $\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$ (**left ordinate**) and the conduction velocity (**right ordinate**). After 7 minutes of application, the contour of the action potential began to alternate with every other beat, thus providing 2 data points on the same time scale. Eventually there was complete block of conduction after 8.5 minutes of application. **B,** time course of l-verapamil (1 μg/ml) effects on the amplitude of $\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$ (**left ordinate**) and conduction velocity (**right ordinate**). Same experiment as in Figure 3, D to F.

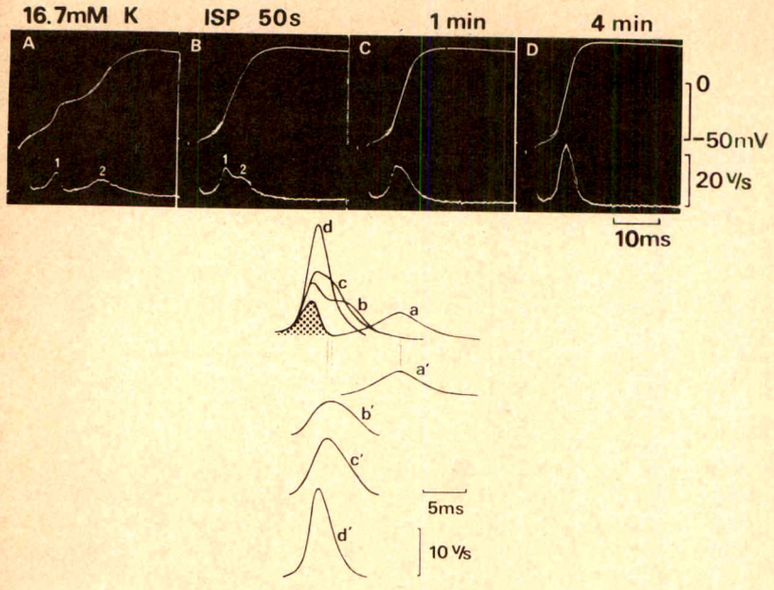

FIGURE 5. Effects of isoproterenol (0.1 μM) on action potential upstroke and the first derivative in 16.7 mM K^+ Tyrode's solution (**upper panels**). **A,** control. **B, C, and D,** 50 seconds, 1 minute, and 4 minutes after application of isoproterenol, respectively. **Numerals 1 and 2** on the lower tracings correspond to $\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$ as depicted in Figure 1A. **Lower panels,** magnified tracings of upstroke velocity. Tracings a, b, c, and d correspond to the bottom tracing in panels A, B, C, and D, respectively. Tracings a′, b′, c′, and d′ were obtained by subtracting $\dot{V}_{max,fast}$ in tracing a (**stippled area**) from tracings a, b, c, and d, respectively, to demonstrate the isoproterenol-induced change in $\dot{V}_{max,slow}$. In this scheme, the $\dot{V}_{max,fast}$ was assumed to be constant during application of isoproterenol, although $\dot{V}_{max,fast}$ itself was actually decreased by the drug (see text). Marked separation of upstroke phase with diminished $\dot{V}_{max,fast}$ in panel A is partly due to a faster rate of stimulation (0.5 Hz) (compare with Fig. 6).

Characteristics of residual fast channel-dependent slow conduction: Figure 3, A to C illustrates typical effects of lidocaine on the upstroke of residual fast channel-dependent action potential and the conduction in K^+-enriched media. In both action potentials in each panel, the drug decreased $\dot{V}_{max,fast}$ with no change in $\dot{V}_{max,slow}$ and the conduction time was also increased (Fig. 3, B and C). Eventually the conduction was blocked, immediately after recording Figure 3C (not shown). This effect was completely reversible (Fig. 3D). The changes in $\dot{V}_{max,fast}$, $\dot{V}_{max,slow}$, and the conduction velocity during action of lidocaine were plotted versus time, in a different preparation (Fig. 4A). It is evident that the conduction velocity decreased in parallel with

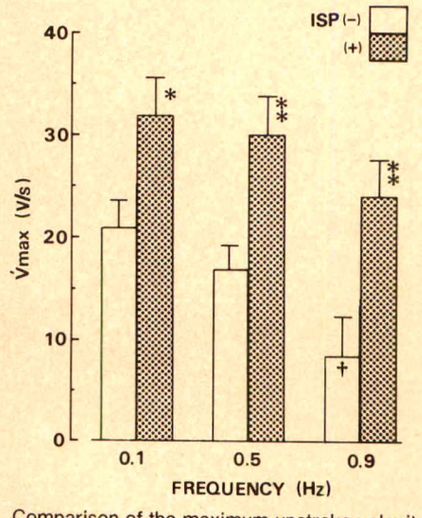

FIGURE 6. Comparison of the maximum upstroke velocity of action potentials in the absence (**open bars**) and presence (**shaded bars**) of isoproterenol (ISP) (0.1 μM) at different stimulation rates (0.1, 0.5, and 0.9 Hz) in 5 preparations each. In these experiments, $\dot{V}_{max}$ was expressed as the amplitude of the larger component out of either $\dot{V}_{max,fast}$ or $\dot{V}_{max,slow}$. Accordingly, $\dot{V}_{max}$ in the absence of isoproterenol (**open bars**) denotes $\dot{V}_{max,fast}$, while $\dot{V}_{max}$ in the presence of isoproterenol (**shaded bars**) represents mostly the amplitude of the $\dot{V}_{max,slow}$ because under these conditions $\dot{V}_{max,slow}$ was markedly increased overriding the $\dot{V}_{max,fast}$ (see Fig. 5, C and D) and $\dot{V}_{max,fast}$ itself was depressed by isoproterenol (see text). **Asterisks** denote significant difference from control value (**open bars**) at each stimulation rate (*$p < 0.05$, **$p < 0.01$); **dagger** indicates significant change ($p < 0.05$) from the control value (**open bar**) at 0.1 Hz. Note that in the presence of isoproterenol there was no significant difference in the $\dot{V}_{max}$ among the different frequencies.

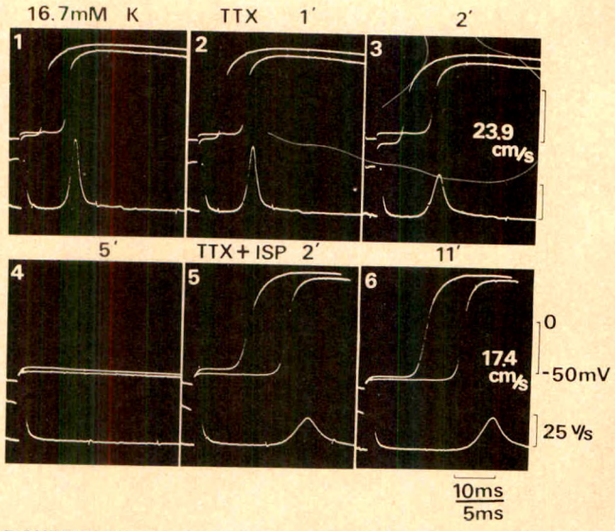

FIGURE 7. Effects of tetrodotoxin (TTX) (1 μM) and isoproterenol (ISP) (0.1 μM) on the action potential upstroke and conduction in 16.7 mM K^+ Tyrode's solution. **1,** control; **2, 3, and 4,** 1, 2, and 5 minutes after application of tetrodotoxin; **5 and 6,** 2 and 11 minutes after the addition of isoproterenol in the continuous presence of tetrodotoxin. In each panel, the bottom tracing represents the first derivative of the proximal (left-side) action potential. In **panel 3,** the microelectrode to some extent extruded from the tissue, thus accounting for a slight decrease in the takeoff potential of the distal fiber (right side), but it returned in panel 4. The **time calibration bar** is 10 ms for action potential tracing and 5 ms for the upstroke velocity in each panel. The interelectrode distance was maintained at 1.6 mm throughout. The conduction velocity was calculated to be 23.9 and 17.4 cm/s in panels 3 and 6, respectively.

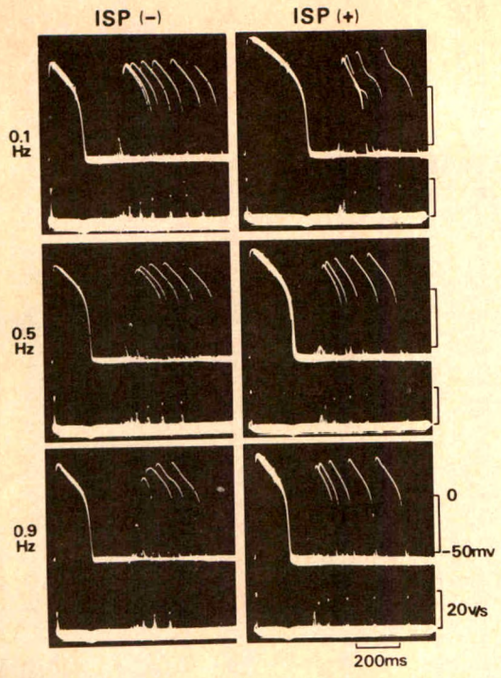

FIGURE 8. Effects of isoproterenol (ISP) (0.1 μM) on repolarization phase in the action potentials elicited by stimulation rates of 0.1, 0.5, and 0.9 Hz in 16.7 m*M* K^+ Tyrode's solution. **Left column,** control records without isoproterenol. **Right column,** effects of isoproterenol. In each panel, the **top tracings** represent the last basic action potential (to the left) and the premature response with variable coupling intervals introduced with every 5 beats of basic stimuli. **Bottom tracings,** first derivative of the action potential.

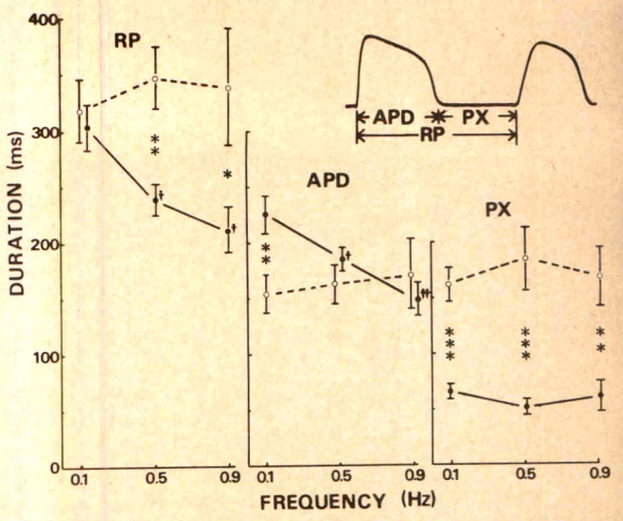

FIGURE 9. Comparison of the durations of postexcitation refractoriness (PX), action potential duration (APD), and effective refractory period (RP) in the absence or presence of isoproterenol (0.1 μM) with different stimulation rates (0.1, 0.5 and 0.9 Hz). **Broken lines** and **open circles** represent the control without isoproterenol; **solid lines and dots** represent effects of isoproterenol. See **inset** for terminology. **Asterisks** denote significant difference from the control value at each stimulation rate (*p <0.05; **p <0.01; ***p <0.001); **daggers** denote significant difference from the duration at 0.1 Hz in the presence of isoproterenol (†p <0.05; ††p <0.01).

the decrease in $\dot{V}_{max,fast}$ while $\dot{V}_{max,slow}$ remained virtually constant until at least 7 minutes after the drug application. Electrical alternation then developed, and there was a prompt decrease in $\dot{V}_{max,slow}$. The alternation continued for about 1 minute before a complete block of the conduction was attained. Similar results were obtained in 2 other preparations.

Conversely, l-verapamil produced little change in $\dot{V}_{max,fast}$ or the conduction time, yet there was a significant decrease in $\dot{V}_{max,slow}$ (Fig. 3, D to F), in keeping with the effects shown in Figure 2, A to C. The time course of the changes during the action of l-verapamil is plotted in Fig. 4B. Comparable results were obtained in 2 other preparations.

Effect of isoproterenol on the upstroke of residual fast channel dependent response: Figure 5A shows an example of the action potential upstroke and the first derivative elicited by a stimulation rate of 0.5 Hz in 16.7 m*M* K^+ concentration, and demonstrates the remarkable step on the way to the peak resulting in a widely split $\dot{V}_{max}$. However the amplitude of $\dot{V}_{max,fast}$ is still larger than that of $\dot{V}_{max,slow}$, indicating that the conduction in this preparation is yet maintained by activation of the residual fast channel. Application of isoproterenol (0.1 μM) quickly shifted the late component ($\dot{V}_{max,slow}$) toward the early one ($\dot{V}_{max,fast}$), as shown in Figure 5B. After 1 minute, both components seemed to fuse (Fig. 5C), and finally $\dot{V}_{max,slow}$ increased considerably, overriding the $\dot{V}_{max,fast}$ (Fig. 5D). At that moment, the step on the upstroke disappeared; the takeoff potentials remained unchanged. The apparent increase in the initial component of split $\dot{V}_{max}$ in Fig. 5B (indicated by "1") was not due to real increase in $\dot{V}_{max,fast}$ but rather to an elevation of the base line produced by both encroachment and increment of the $\dot{V}_{max,slow}$ component (indicated by "2"). The reason was that much lower concentrations of isoproterenol (0.01 to 0.05 μM) always increased $\dot{V}_{max,slow}$ while decreasing $\dot{V}_{max,fast}$ in all 6 preparations tested. Thus isoproterenol produced separate action on the split $\dot{V}_{max}$, that is, an increase in $\dot{V}_{max,slow}$ while decreasing $\dot{V}_{max,fast}$.

The mode of action of isoproterenol on the upstroke phase differed when the stimulation rate was changed. As shown in Figure 6 (open bars), the maximum upstroke velocity of the action potentials in the absence of isoproterenol ($\dot{V}_{max,fast}$) decreased with increase in the stimulation rate from 0.1 to 0.9 Hz. The addition of isoproterenol (0.1 μM) increased the $\dot{V}_{max}$, the peak of which is now composed of $\dot{V}_{max,slow}$ (see Fig. 5, C and D), in all stimulation rates but the increment tended to be remarkable at the higher stimulation rates.

The findings shown in Figures 5 and 6 suggest that the main channel responsible for the slow conduction in the resting potentials of about −58 mV could be changed from the fast to the slow channel during application of isoproterenol, with a conduction velocity comparable to or even faster than that before the application. Figure 7 shows an example of a change in conduction velocity during which time the contributing channels to the slow conduction were altered from the "residual fast" to the "slow" channel with the application of isoproterenol (0.1 μM). Panel 1 (top tracings)

shows action potential upstroke taken from 2 microelectrodes along the preparation in 16.7 m*M* K^+ media, and the bottom tracing denotes the first derivative of the action potential upstroke proximal to the stimulation electrodes (left-hand upstroke). To obtain the slowest possible conduction velocity due to activation of the residual fast channel, we added tetrodotoxin (1 μM) to the preparation (between panels 1 and 2), and this resulted in a prolongation of the conduction time with decreased $\dot{V}_{max}$ (panels 2 and 3). After 5 minutes of the tetrodotoxin treatment, conduction of the impulse was totally blocked and there was a loss of membrane excitability (panel 4). The conduction velocity measured just before development of the conduction block was calculated to be 23.9 cm/s. The addition of isoproterenol between panels 4 and 5 led to a rapid recovery in the generation of action potentials and the conduction (17.4 cm/s) (panels 5 and 6). It is evident that the slow conduction recorded in Figure 7, panel 3 is mediated by activation of the residual fast channel while the slow conduction in Figure 7, panel 6 is induced by activation of the slow channel, since in the latter situation the fast sodium (Na^+) channel should have been completely inactivated by a combination of increased K^+ concentration (16.7 m*M*) plus tetrodotoxin.

Effects of isoproterenol on repolarization in the residual fast channel dependent response: Figure 8 demonstrates the action potentials elicited at different stimulation frequencies of 0.1, 0.5, and 0.9 Hz followed by premature action potentials, with variable coupling intervals. In the absence of isoproterenol (left column), there was no significant difference in the duration of the action potential among different stimulation rates, and the earliest premature response lagged about 180 ms after the end of phase 3 of the basic action potential, in all stimulation rates. We term this interval of no response in phase 4 *postexcitation refractoriness*, which could be due to increased reactivation time of the fast Na^+ channel produced by partial depolarization.[20] In contrast, during the action of isoproterenol, the action potential duration was prolonged at a low stimulation rate (0.1 Hz) and shortened at a high stimulation rate (0.9 Hz). The action potential duration at the intermediate stimulation rate (0.5 Hz) remained much the same. The postexcitation refractoriness was markedly shortened with all the stimulation rates used. This implies that application of isoproterenol leads to a recovery of several properties characteristic of normal ventricular muscle in a physiologic K^+ concentration, that is, rate-dependent shortening of action potential duration[21] and lack of postexcitation refractoriness,[22] which could have been abolished in K^+-enriched media.

The results obtained from 7 similar experiments are summarized in Figure 9. Isoproterenol significantly shortened postexcitation refractoriness by about 120 ms in all stimulation rates, lengthened the action potential duration at 0.1 Hz, and eventually shortened the effective refractory period (the sum of action potential duration and postexcitation refractoriness) at the rates of 0.5 and 0.9 Hz. In the present experiments, stimulation rates of over 0.9 Hz were not applied systematically as many preparations did not consistently respond to such rapid stimulation in K^+-enriched media.

Discussion

In the present study we found that, in 16.7 m*M* K^+-enriched media, the resting potential of guinea pig ventricular muscle was depolarized to about −58 mV and that the action potential upstroke exhibited a step-like discontinuity on the rising phase which was characterized by 2 distinct components of $\dot{V}_{max}$. The early $\dot{V}_{max,fast}$ component was produced by activation of the residual fast channel, while the late $\dot{V}_{max,slow}$ component was due to activation of the slow channel. The amplitude of the former is about 3 times that of the latter. The conduction velocity in this situation was slow (30 to 35 cm/s) and the impulses were transmitted by activation of the partially inactivated Na^+ channel (fast response) and not by the slow channel (slow response). It is well known that the slow conduction in severely depolarized fibers less than −40 mV is dependent on the activation of slow channel.[9] So far as we know there have been no systematic studies on slow conduction at resting potentials of −50 to −60 mV where the fast sodium channels could be still operating.

Two components of action potential upstroke in the presence and absence of isoproterenol: It has been suggested that the action potential upstroke of frog atrial[23] and ventricular muscle[24] might be composed of 2 essentially different components under physiologic K^+ concentrations. In mammalian cardiac fibers, a step on the upstroke with a bifid $\dot{V}_{max}$ has been reported in the case of the guinea pig ventricle after treatment with tetrodotoxin in normal K^+ concentration.[19] The split $\dot{V}_{max}$ demonstrated in the present study may be accounted for on the same basis of the known phenomena. In guinea pig ventricular muscle, the contour of first derivative of the action potential upstroke appeared sharp and single-peaked in normal K^+ concentration. Conceivably, in mammalian cardiac tissue, the second slow component can be disclosed only when the fast Na^+ channel has been considerably inactivated by either increasing K^+ concentration (this study) or by adding tetrodotoxin.[19] A distinct step on the rising phase was reported also in the case of Purkinje fibers in which the fast channel was depressed by elevating K^+ concentrations.[25] The present results indicate that the first upstroke component in guinea pig ventricular muscle is produced by activation of fast Na^+ channel, while the second component is due to the slow channel (Fig. 3). The lack of depressant action of d,l-verapamil on the $\dot{V}_{max}$ has been reported in ventricular fiber depolarized to between −55 and −60 mV by potassium.[26] In 16.7 m*M* K^+ concentration, the amplitude of $\dot{V}_{max,fast}$ was about 3 times that of $\dot{V}_{max,slow}$, and the conduction velocity correlated with the amplitude of $\dot{V}_{max,fast}$ and never with the $\dot{V}_{max,slow}$ (Fig. 4). These findings suggest that the conduction under this situation is maintained by the activation of fast Na^+ channels, although most would be inactivated due to a reduction in the membrane potential ("residual fast channel").

However, when isoproterenol was added to the per-

fusing media, the ionic channels related to the conduction readily changed from the residual fast to the slow channel but without change in the resting potential. Catecholamines restore the action potentials in atrial muscle[27] and Purkinje fibers,[25,28] in which the fast Na^+ channel had been completely inactivated by increased K^+ concentrations. The mechanism underlying the isoproterenol-induced increase in the $\dot{V}_{max,slow}$ (present study) may be the same.

Conduction velocity in excitable tissue is determined by a variety of factors, both passive and active.[29] In mammalian cardiac tissues, the action potential amplitude and the $\dot{V}_{max}$ were considered the most important factors underlying variation in conduction velocity,[30] when the resting potential was less negative than −70 mV.[31] The present study (Fig. 4) lends support to the idea that the $\dot{V}_{max}$ is the major determinant of conduction velocity, at least in K^+-depolarized fibers.

Effects of lidocaine and verapamil on residual fast channel dependent conduction: Using potassium-sensitive electrodes, Hill and Gettes[2] reported that extracellular K^+ concentrations at the center of the ischemic zone in swine hearts increased to a mean value of 10 m*M* (range 5.5 to 16.3) within 5 to 8 minutes after acute coronary occlusion. Comparable data were also presented by Hirche et al,[3] who found that during a short period of occlusion (within 10 minutes) two thirds of the experimental animals developed ventricular tachyarrhythmias including fibrillation. Similar increases of K^+ concentrations were reported in the case of perfused rabbit hearts in which the septal branch of the left coronary artery was occluded.[32]

Although we used nearly maximal K^+ concentrations (16.7 m*M*) reported to be present in the very early phase of myocardial ischemia (within 10 minutes after occlusion), the conduction always depended on activation of the residual fast channel when the perfusate was devoid of catecholamine. Thus, the reentrant excitation evident in the very early phase of regional ischemia[32] may have been due to the slow conduction and unidirectional block through the depressed fast channel. However, since low pH (6.4) and hypoxia (partial pressure of oxygen <30 mm Hg) influenced both $\dot{V}_{max,fast}$ and $\dot{V}_{max,slow}$ with a resultant decrease in the conduction velocity,[33] the final conclusion on the ionic channels responsible for the reentry in in vivo ischemic hearts should await further study.

In most preparations, the conduction velocity in the absence of isoproterenol ranged from 30 to 35 cm/s, under conditions of 16.7 m*M* K^+ concentration (Fig. 4). This degree of conduction velocity appeared slow enough for the maintenance of reentrant arrhythmias in porcine and canine hearts.[34] In that study complete circus movement was convincingly demonstrated along the circle with a diameter of approximately 1 to 2 cm and a revolution time of approximately 120 to 170 ms, thus implying that the calculated conduction velocity could be between 20 and 50 cm/s.

The conduction velocity decreased still further in the presence of a fast channel blocker such as lidocaine or tetrodotoxin, down to about 20 cm/s just before complete conduction block ensued (Fig. 3, 4, and 7). Such marked depressant action of lidocaine on the depolarized ventricular muscle may be explained by a shift of the steady-state $\dot{V}_{max}$-E_m relationship in a hyperpolarizing direction, or the slowed recovery kinetics of $\dot{V}_{max}$ by the drug, or both.[35] However, lidocaine also increases the time-independent outward K^+ current (i_{K1})[36] and reduces the tetrodotoxin-sensitive "window" current[37] in Purkinje fibers. The increase in i_{K1} may decrease the conduction velocity through a reduction in the membrane resistance (shortening of length constant). However, this effect seems to have less importance, if any, since we measured the conduction velocity in high K^+ media in which the membrane resistance should have already been very low.

In the Purkinje fibers, Brennan et al[25] found that lidocaine at a concentration of 5 and 20 μg/ml reduced $\dot{V}_{max}$ and conduction velocity of "depressed fast response action potentials" in which the resting potentials were depolarized to about −60 mV by elevating K^+ concentrations. In contrast, the drug had little or no effect on the slow response elicited in a Na^+-free, Ca^{2+}-rich solution or a high K^+ solution containing norepinephrine. Their findings closely resemble our observations in the ventricular muscle, although they did not direct particular attention to the splitting of $\dot{V}_{max}$ and did not calculate the actual conduction velocity.

Modification of the residual fast channel dependent response by isoproterenol and clinical implication: After complete block of the residual fast channel dependent slow conduction by tetrodotoxin, the addition of isoproterenol reproduced the conduction with a similar conduction velocity (Fig. 7). Theoretically, the latter conduction must depend solely on an activation of the slow channel.[9,25] Therefore, it seems likely that there is no discernible difference between the minimum conduction velocity due to fast channel activation and the maximum conduction velocity due to activation of the catecholamine-enhanced slow channel. If such is indeed the case, the dominant channel responsible for slow conduction and unidirectional block in the reentrant pathway may be changed from the residual fast channel to the slow channel or vice versa without change in conduction velocity when local concentrations of catecholamine are altered. This could happen in a patient with acute myocardial infarction in which sympathetic tone increased transiently.[8]

Although there are no available reports on local differences in catecholamine concentration within the ischemic myocardium, significant differences in the norepinephrine content have been reported in the canine left ventricle under control conditions.[7] Should the local concentrations of catecholamine not be homogeneous within the ischemic tissue, the likelihood of reentrant excitation may alter according to the heart rate, because with relatively rapid rates (≥0.5 Hz), the effective refractory period at a site of high norepinephrine concentration should be shorter than that in a low concentration (Fig. 9). This may result in a nonuniform recovery of excitability, one of the important factors in initiation and maintenance of ventricular tachyarrhythmias.[34]

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Vessel Wall Arachidonate Metabolism After Angioplasty: Possible Mediators of Postangioplasty Vasospasm

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The mechanism of postangioplasty vasospasm is uncertain. It was postulated that a reduction in vasodilator prostaglandin I_2 (PGI_2) or prostaglandin E_2 (PGE_2) or an increase in vasoconstrictor hydroperoxy acids might contribute to spasm of a dilated artery. Twelve mongrel dogs were anesthetized, intubated, and mechanically ventilated. Heart rate and aortic pressures were continuously monitored and arterial blood gases maintained within physiologic limits. A single carotid artery was dilated in each animal (4 atm × 1 minute × 3) using nonexpandable polyethylene balloon catheters with inflated balloon diameters 50 to 100% larger than the internal arterial lumen. The opposite carotid artery served as a control. In 4 animals, aspirin (10 mg/kg, intravenously) was injected 30 minutes before dilation. Sixty minutes after dilation, animals were heparinized and the carotid arteries carefully removed. The in vitro conversion of carbon-14(^{14}C)-arachidonic acid (AA) to 6-keto $PGF_{1\alpha}$ (PGI_2), PGE_2, and 12L-hydroxy-5,8,10,14-eicosatetraenoic acid (HETE) was determined using thin-layer radiochromatography. Angioplasty caused a 70% decrease in vessel wall PGI_2 production and a 44% decrease in PGE_2 production ($n = 4$, $p < 0.05$). Reductions in in vitro conversion of ^{14}C-AA to PGI_2 and PGE_2 induced by angioplasty were comparable to that produced by cyclooxygenase inhibition with aspirin. Angioplasty, in addition, caused a 104% increase in vessel wall HETE production ($n = 4$, $p < 0.05$). Therefore, angioplasty results in a local derangement of AA metabolism characterized by decreases in vasodilator prostaglandins and increases in vasoconstrictor hydroperoxy acids. These local changes may contribute, in part, to sudden arterial occlusion after angioplasty.

Vasospasm associated with coronary angiography and transluminal angioplasty is a serious complication requiring prompt treatment.[1–4] Sudden occlusion of the dilated coronary artery occurs in 3 to 8% of cases, often necessitating emergency coronary artery bypass surgery.[5] The mechanism by which postangioplasty vasospasm occurs is not known.

Angioplasty is known to produce its effect in part by overstretching the arterial media. In this respect, vasospasm after angioplasty is a form of traumatic arterial spasm.[6] Hunter[7] first described the property of vasoconstriction after arterial trauma in 1835. Others[8] have documented reflex vasoconstriction induced by arterial stretching.

Numerous studies have investigated potential mechanisms of vasospasm.[6,9–12] Possible mediators include vasoactive substances such as the prostaglandins (PGI_2 and PGE_2) and hydroperoxy acids produced by the coronary arteries as well as thromboxane A_2 (TxA_2) released during platelet activation.[13–19] Decreased production of vasodilator prostaglandins or increased production of the vasoconstricting hydroperoxy acids by the vessel wall may be associated with vasospasm.[13,14,19]

The prostaglandins PGI_2 and PGE_2, both vasodilators in vivo, are produced in vascular endothelium and medial smooth muscle.[20,21] We postulated that damage to the vessel wall which occurs during angioplasty[22,23] could decrease local prostaglandin production or increase local hydroperoxy acid formation and lead to

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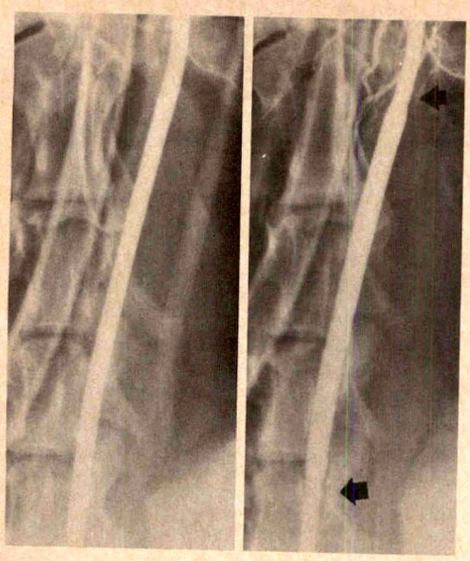

FIGURE 1. Canine carotid angiogram. Control vessel diameter is 3.7 mm (**left**). After dilation, the arterial diameter has increased to 4.7 mm (**right**).

vasospasm. To test our hypothesis, we determined the effect of arterial dilation on vessel wall arachidonic acid metabolism in canine carotid arteries.

Methods

Animal preparation: Twelve mongrel dogs weighing 15 to 30 kg were sedated with fentanyl (40 mg/kg, intramuscularly) and droperidol (2 mg/kg, intramuscularly) (Innovar-Vet, Pitman-Moore) and anesthetized with sodium pentobarbital (20 mg/kg, intravenously). The animals were mechanically ventilated with room air (Harvard respirator) and anesthesia was maintained by periodic pentobarbital injections.

Catheterization was accomplished by use of femoral artery cutdown. Aortic pressure was measured using a fluid catheter connected to a Statham P23Db strain gauge and was recorded with a lead II electrocardiogram on a Honeywell (model 1858) multichannel recorder. During the control period and 60 minutes after angioplasty, arterial blood samples were measured for pH, partial pressure of carbon dioxide (PCO_2) and oxygen (PO_2) (Instrumentation Laboratory model 113 analyzer), and hematocrit. Selective carotid angiograms were obtained during the control period and immediately after dilation by the rapid manual injection of 7 ml of 60% meglumine diatrizoate (Hypaque® 60, Winthrop). A single carotid artery in each animal was dilated (4 atm × 1 minute × 3) using nonexpandable polyethylene balloon catheters (Meditech, Watertown, Massachusetts). The inflated balloon diameters were 50 to 100% larger than the internal arterial lumen. The length of each dilated segment ranged from 5 to 10 cm (Fig. 1). Oversized balloons were used to simulate the clinical situation in which significant medial stretching is produced by dilation of the stenotic atherosclerotic artery.[24]

In 4 animals, acetylsalicylic acid (10 mg/kg) prepared as a sodium bicarbonate buffered solution (pH 7.0 to 7.5) was injected slowly 30 minutes before dilation. Samples for serum salicylate levels were drawn during the control period and 60 minutes after aspirin administration. Sixty minutes after dilation, each animal in the study was heparinized (300 units/kg) and both carotid arteries were carefully dissected out. Care was taken to avoid blunt trauma to the carotid arteries during their removal. After dissection, the animals were killed with an overdose of sodium pentobarbital.

Arachidonic acid metabolism: Each carotid artery was divided in vitro into a dilated segment and adjacent segments proximal and distal to the dilated portion. The opposite undilated carotid artery was taken as a control. The fresh specimens were placed in a buffered solution (Hanks' Balanced Salt Solution [HBSS], pH 7.4 containing no Ca^{2+} or Mg^{2+}) and loose adventitia was carefully removed.

In 4 animals, carotid artery 6-keto $PGF_{1\alpha}$ (PGI_2) and PGE_2 production was determined. In 4 other animals, the production of 12-L-hydroperoxy-5,8,10,14-eicosatetraenoic acid

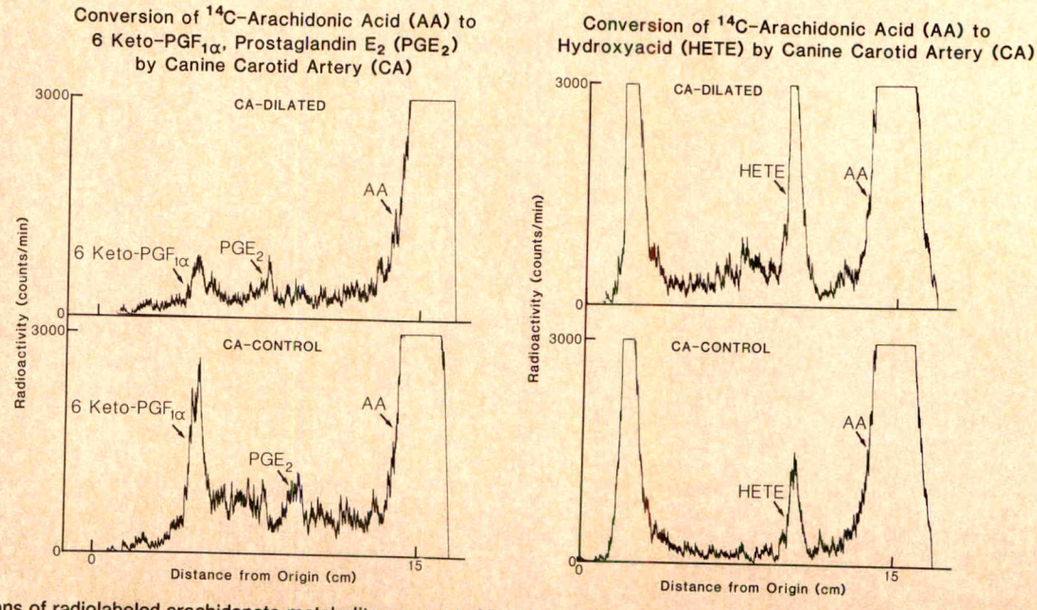

FIGURE 2. Scans of radiolabeled arachidonate metabolites separated by thin layer chromatography. **Left,** peaks for PGI_2 and PGE_2; **right,** HETE for a control and dilated carotid artery. In the dilated artery, PGI_2 and PGE_2 production is decreased while HETE production is augmented.

(HPETE) was determined by measuring its stable hydroxy-metabolite (12-HETE). In the aspirin-treated group, 6-keto $PGF_{1\alpha}$, PGE_2, and HETE production was measured in 2 animals each.

For measurement of arachidonic acid metabolism, each reaction mixture containing approximately 185 ± 35 mg of finely chopped tissue was incubated in 1 ml of regular HBSS (pH 7.4) at 37°C in a shaking waterbath for 60 minutes with 1 μg of labeled arachidonic acid (1-^{14}C-AA; New England Nuclear, Boston, Massachusetts).[25] At the end of the experiment, 1 ml of ethyl acetate was added to each reaction mixture and acidified with 0.5 *M* citric acid to a pH of 3.5. After thorough mixing, the ethyl acetate layer was separated and the reaction mixture was once more extracted with an equal volume of ethyl acetate. Fractions of the organic phase were pooled, concentrated over nitrogen, and saved for further analysis.

Separation of various metabolites: Pooled concentrates were plated on a silica gel G plate. The metabolites PGE_2 and 6-keto-$PGF_{1\alpha}$ were separated with the organic phase of a solvent system comprised of ethyl acetate/2,2,4-trimethyl pentane/acetic acid/water (11:5:2:10 volume/volume).[25] HETE formed by way of the lipoxygenase pathway was separated using a different solvent system consisting of petroleum ether (60 to 70°C)-diethyl ether-acetic acid (60:39:1).[26] Authentic standards of PGE_2 and 6-keto-$PGF_{1\alpha}$ were cochromatographed for identification of the AA metabolites. Radioactivity was monitored with a Berthold radiolabel scanner and quantitation was achieved by separation of the spots containing radioactivity and counting in a Beckman LS3133T scintillation counter. Values for 6-keto $PGF_{1\alpha}$, PGE_2, and HETE are expressed as percent conversion of ^{14}C-AA.

Statistical methods: In vitro vessel wall AA metabolism was analyzed using analysis of variance for repeated measures. Hemodynamic and blood gas data were analyzed using Student's 2-tailed *t* test adjusted for performing multiple tests on correlated data (Bonferroni method).[27] Values are expressed as mean ± standard error (SE). The criterion for statistical significance was $p < 0.05$.

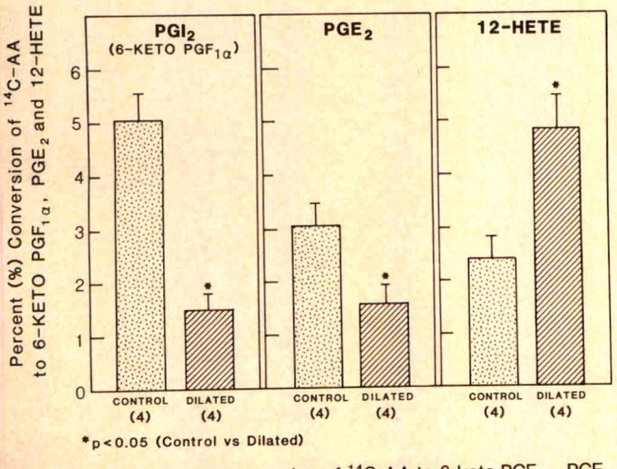

FIGURE 3. Vessel wall conversion of ^{14}C-AA to 6-keto $PGF_{1\alpha}$, PGE_2, and 12-HETE in nonaspirin-treated dogs (mean ± standard error of the mean). The production by the canine carotid artery of the vasodilating prostaglandins, PGI_2, and PGE_2 is significantly reduced after angioplasty. Production of the potent vasoconstrictor 12L-hydroperoxy-5,8,10,14-eicosatetraenoic acid (HPETE) is significantly increased by angioplasty. Note: 12-HPETE is determined by measuring its stable hydroxy-metabolite (12-HETE).

Results

Arachidonic acid metabolism: Figure 2 depicts an original scan of the radiolabeled AA metabolites separated on thin layer plates. Values for percent conversion of ^{14}C-AA to 6-keto $PGF_{1\alpha}$ (PGI_2), PGE_2, and 12-HETE are shown in Table I. Angioplasty caused a significant decrease in vessel wall PGI_2 (70 ± 6%) and PGE_2 (43 ± 14%) production ($p < 0.05$) relative to control (Fig. 3). At the same time, vessel wall HPETE production was significantly elevated (104 ± 13%) compared with control values ($p < 0.01$).

The reduction in PGI_2 and PGE_2 production after angioplasty was comparable to that produced by cyclooxygenase inhibition with aspirin. In aspirin-treated animals, conversion of ^{14}C-AA to 6-keto $PGF_{1\alpha}$ and PGE_2 in the undilated artery was 1.30 and 1.86%, respectively (n = 2). In the dilated artery, values for 6-keto $PGF_{1\alpha}$ and PGE_2 were 0.86 and 1.17%, respectively (n = 2). Control vessel wall HETE production in aspirin-treated animals was 0.89%. In the dilated artery, HETE production was 2.20% (Table II).

Before aspirin administration, serum salicylate levels in aspirin-treated animals (n = 4) were all <2 mg/100 ml, that is, below the sensitivity of our laboratory. The

TABLE I Nonaspirin-Treated Group Conversion of ^{14}C-Arachidonic Acid to 6-Keto $PGF_{1\alpha}$, PGE_2, and 12-HETE

	6-Keto $PGF_{1\alpha}$ (PGI_2)	PGE_2	12-HETE
Percent conversion			
Carotid artery			
Opposite (control)	5.04 ± 0.55	3.09 ± 0.40	2.39 ± 0.39
Dilated	1.49 ± 0.33*	1.61 ± 0.65†	4.78 ± 0.59*
Adjacent (nondilated)	2.48 ± 0.32*	2.65 ± 0.73	3.53 ± 0.49*

Values expressed as mean ± standard error, n = 4.
Comparison of dilated versus control and adjacent versus control carotid artery using single repeated measures analysis of variance: *$p < 0.01$, †$p < 0.05$ (p values for simultaneous repeated measures analysis of variance were $p < 0.007$ [12-HETE]; $p < 0.08$ [PGI_2]; $p = 0.14$ [PGE_2]).
HETE = hydroxyeicosatetraenoic acid; PGE_2 = prostaglandin E_2; $PGF_{1\alpha}$ = prostaglandin $F_{1\alpha}$; PGI_2 = prostaglandin I_2.

TABLE II Aspirin-Treated Group Conversion of ^{14}C-Arachidonic Acid to 6-Keto $PGF_{1\alpha}$, PGE_2, and 12-HETE

	6-Keto $PGF_{1\alpha}$ (PGI_2)	PGE_2	12-HETE
Percent conversion			
Carotid artery			
Opposite (control)	1.30 (1.64–0.96)	1.86 (2.59–1.14)	0.89 (0.96–0.82)
Dilated	0.86 (0.68–1.05)	1.17 (1.12–1.22)	2.20 (2.54–1.86)
Adjacent (nondilated)	0.70 (0.78–0.61)	1.20 (1.2–1.2)	1.52 (1.51–1.54)

Values expressed are means, n = 2.
Data presented for dogs are in parentheses.
Abbreviations as in Table I.

mean salicylate level 60 minutes after aspirin administration was increased to 3.8 (3.0 to 4.2) mg/100 ml ($p < 0.05$).

Hemodynamic characteristics: No differences were noted between the hemodynamic values from the aspirin and nonaspirin treated groups; therefore, the values from both groups were combined. Mean aortic pressure (97 ± 5 mm Hg), heart rate (113 ± 10 beats/min), PO_2 (97 ± 6 mm Hg), PCO_2 (34 ± 3 mm Hg), pH (7.43 ± 0.02), and hematocrit (41 ± 2%) were maintained within physiologic limits (n = 12). No significant differences were noted 60 minutes after angioplasty, with the exception of aortic pressure which was increased to 118 ± 7 mm Hg ($p < 0.05$).

Discussion

Arterial tone is regulated by a complex combination of neural and humoral factors. Among the humoral mediators of vascular tone are substances such as norepinephrine, adenosine, bradykinin, and prostaglandins which cause either contraction or relaxation of vascular smooth muscle. In recent years, it has been suggested that the prostaglandin endoperoxides and thromboxanes play a significant role in modulating arterial tone, particularly in the coronary circulation.[28] Decreased levels of the vasodilators, PGI_2, PGE_2, and/or PGE_1 or increased levels of vasoconstricting substances such as TxA_2 could be responsible in part for both traumatic arterial spasm and vasospastic angina. PGI_2 and PGE_1 have been used, in fact, to treat certain forms of vasospasm.[29,30]

However, in addition to the well-established pathways of prostaglandin formation, another more recently discovered enzyme—lipoxygenase—has been shown to convert arachidonic acid to various hydroperoxy acids which may have vasoregulatory effects: 12-HPETE produced in the vessel wall[16] has been shown to constrict coronary arteries[17] and rabbit aortic strips[18] and, thus, may contribute to vasospasm. In addition, HPETE inhibits the production of the vasodilator PGI_2.[31]

In our study, PGI_2 and PGE_2 production were significantly decreased in the dilated artery. The decrease in prostaglandin activity was similar to that produced by cyclooxygenase inhibition with aspirin. Aspirin in doses >5 mg/kg may produce vasoconstriction by decreasing PGI_2 production, enhancing platelet accumulation, or both.[32] Endothelial denudation after angioplasty may produce the same effect, that is, decreased PGI_2 production and increased platelet aggregation onto the injured artery with release of thromboxane from platelet thrombi.[30] These factors could contribute to sudden closure of the dilated artery after angioplasty, due either to platelet accumulation or vasospasm.

We found local vessel wall HPETE production to be significantly elevated after angioplasty. Since the vasoconstrictive properties of HPETE are well established, it is not unreasonable to speculate that lipoxygenase products may contribute to vasospasm. The mechanism, however, by which angioplasty causes such a large increase in HPETE production is not clear. It is possible that angioplasty, by denuding the vascular endothelium, removes the major site of PGI_2 production while leaving less affected components of the vessel wall which preferentially metabolize arachidonic acid by way of the lipoxygenase pathway. Figure 4 proposes 1 sequence of events by which vasospasm may be produced after angioplasty.

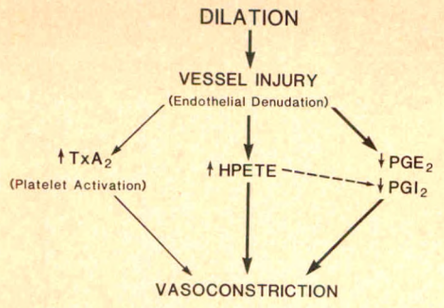

FIGURE 4. Possible mechanism of vasospasm after angioplasty. Arterial dilation which is characterized by medial overstretching and endothelial denudation results in decreased production of the vasodilating prostaglandins PGI_2 and PGE_2 and increased production of the vasoconstrictor hydroperoxy eicosatetraenoic acid (HPETE). HPETE, in turn, further inhibits PGI_2 production. In addition, platelets accumulating at the site of dilation may release thromboxane A_2 (TxA_2), another potent vasoconstrictor.

We also noted in our study that values for PGI_2, PGE_2, and HPETE in the arterial segment adjacent to the dilated portion were generally intermediate between those of the dilated and opposite control artery. The reason for this is not known. It is possible that angioplasty may alter arterial metabolism over a large segment so that the same factors producing local derangement of arachidonic acid metabolism may produce an identical though less intense response remote from the dilation site. It is possible that the hypertonic contrast media used during angiography could affect endothelial cell function and, thus, prostaglandin production. In our study, however, angiograms of the opposite undilated artery were also obtained in 4 animals without altering vessel wall arachidonate metabolism. Furthermore, the small volumes (7 ml) of contrast media used in our study were rapidly diluted by arterial flow.

Aspirin in a dose of 10 mg/kg caused an approximately 50% decrease in vessel wall HETE generation in both control and dilated arteries. The relative increase in HETE production in the dilated artery was preserved, however. While low doses of aspirin (5 mg/kg) do increase HETE production by selectively inhibiting cyclooxygenase, our findings are consistent with other studies which have shown that larger aspirin doses (5 mM = 30 mg/kg) produce peroxidase inhibition as well,[33] resulting in decreased HETE levels, as was observed in our study.

This study has focused on just some of the potential mechanisms for control of vascular tone in damaged arterial tissue. Our results indicate that vascular spasm in some cases may result from reductions in vasodilator prostaglandins or an increase in vasoconstrictor hydroperoxy acids, or both. The extent to which these changes contribute to clinical vasospasm in stenotic

atherosclerotic arteries is unknown. However, since PGI_2 production is known to be reduced in atherosclerotic arteries,[31] even minor reductions may predispose these vessels to spasm. In addition, loss of endothelial cells from the arterial lumen after angioplasty and altered arachidonate metabolism in the vascular wall could convert endothelial dependent endogenous vasodilators (such as acetylcholine and bradykinin) into vasoconstrictors.[34]

Acknowledgment: We acknowledge the technical assistance of Joseph Rysavy, Barbara Borgwardt, Colleen McAdaragh, and K. R. Reddy, and the expert secretarial assistance of Sandra Sondelski.

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Cryosurgery of the Fetal Ductus Arteriosus

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The effects of cryosurgical treatment of the fetal ductus arteriosus (DA) on the structure and function of the neonatal DA are assessed for the first time. A cryosurgical probe, cooled with nitrous oxide, was used to freeze the wall of the DA in 5 fetal lambs. Six fetal lambs were used as control animals. After birth, all the cryosurgically treated lambs had a patent DA whereas all the control lambs had a closed DA. Only the cryosurgically treated group had these histologic findings: calcific deposits, necrosis, and focal ganglion cell necrosis in the outer one third to two thirds of the media with a decrease or loss of muscle cells and elastic fibers. This study suggests the feasibility of developing a cryosurgical approach for maintaining patency of the DA.

Persistent patency of the ductus arteriosus (DA) may be lifesaving in infants with certain forms of congenital heart disease.[1–3] The only available technique that results in persistent DA patency for a period of months is formalin infiltration of the wall.[1] Although often successful, the desired effect may not be achieved or may disappear within weeks. This study examines for the first time how freezing the fetal DA affects the morphology and the closure of the neonatal DA. Cryosurgery of large arteries and the aorta has not been associated with any complications.[5,6] We used a cryoprobe that had been successful in inducing atrioventricular block and interrupting accessory pathways.[7,8] The fetal lamb was chosen because (1) the effects of DA formalin infiltration were explored initially in the lamb, and (2) patency of the fetal DA is a normal physiologic condition. The lamb is able to recover from surgery before the potentially devastating hemodynamic effects of a widely patent DA are superimposed on the normal neonatal circulation.

Methods

Surgical preparation: Eleven mixed-breed ewes with age-dated pregnancies (5 in the cryosurgically treated group and 6 in the control group) were anesthetized with intravenous ketamine (1 to 4 mg/ml). The uterus was exposed through a low midline abdominal incision, a hysterotomy was made over the fetal left lateral chest, and a thoracotomy performed through the third intercostal space. The parietal pericardium was opened, and using blunt dissection the DA was exposed from its origin at the left main pulmonary artery to its insertion in the descending aorta.

The cryosurgical handheld tool (Frigitronics, Shelton, Connecticut) was cooled by expansion of nitrous oxide within the probe tip. The instrument had an insulated handle and a probe that was 4.3 cm long and ended in a flat circular tip 5 mm in diameter. In both the cryosurgically treated group and the control group, the tip was held for 90 seconds against the DA and then moved to an adjoining area. This procedure was repeated until the entire surface of the exposed DA, from the main pulmonary artery to the aorta, had been covered by these overlapping circles. In the cryosurgically treated group the tip was held at −60°C for the 90 second period. A 1 to 1.5 mm edge of frost extended over the surface of the DA beyond the edge of the probe and then disappeared when the tip was returned to room temperature. Although the depth of the wall subjected to freezing was unknown, the tip was frozen to the surface and could not be removed until the temperature was increased. The shape of the available probe would only allow treatment of the exposed DA surfaces. The period of treatment lasted approximately 20 to 25 minutes before the incisions were closed and anesthesia was discontinued. The subsequent care of the 2 groups of ewes was the same.

Cardiac catheterization: Three cryosurgically treated lambs, were catheterized at the following ages: 3 hours; 3 days; and 1 lamb at 4, 14, and 93 days of age. One control lamb underwent cardiac catheterization on the third day of age. Shunting through the DA was estimated with use of Fick and indocyanine green dye techniques. Hypaque (1 to 1.25 ml/kg) was used for the aortogram.

Necropsy: The lambs were killed using intravenous ketamine (100 mg/kg). In the cryosurgically treated group, 2 died in the first 2 hours of life. The others were killed at 6 hours, 5 days, and 93 days of age. In the control group, 2 were killed at 3 hours of age, and the others were killed at 4 hours, 1, 3, and 5 days of age. The ascending and transverse aortic arch, pulmonary trunk, DA, and descending aorta were removed, fixed

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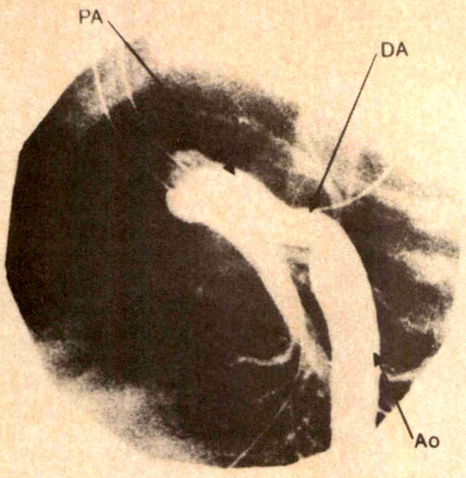

FIGURE 1. Aortogram of cryosurgically treated lamb (see text). The site of injection was the descending aorta (Ao). The main pulmonary artery (PA) and ductus arteriosus (DA) are well filled.

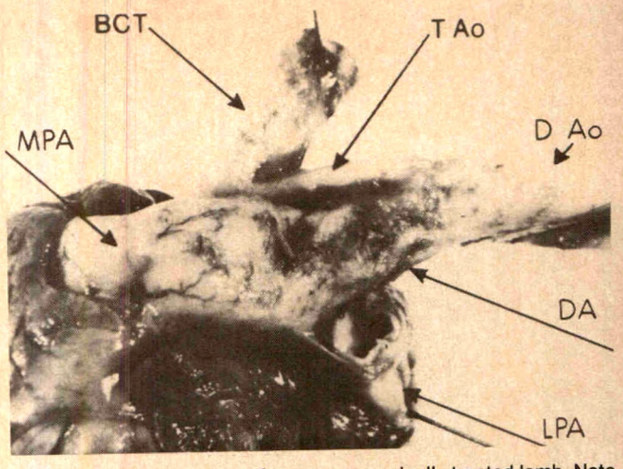

FIGURE 2. Gross specimen from a cryosurgically treated lamb. Note the appearance of the ductus arteriosus (DA), (see text). BCT = brachiocephalic trunk; DAo = descending aorta; LPA = left pulmonary artery; MPA = main pulmonary artery; TAo = transverse aortic arch.

in 10% buffered formalin, and processed for light microscopy. Sections were stained with hematoxylin and eosin, Masson's trichome (for collagen), and by the Verhoeff-van Geison method (for elastic tissue). Two pathologists evaluated them independently.*

Results

Lambs: The cryosurgically treated lambs were operated on at gestational ages ranging from 115 to 135 days of age (127 ± 8, mean ± 1 standard deviation). The control lambs were operated on at ages ranging from 121 to 134 days (mean 128 ± 5). The cryosurgically treated lambs were delivered 17 ± 9 days after surgery. The interval for the control group was 16 ± 5 days. The mean gestational age at delivery of the cryosurgically treated group was 145 ± 4 days and for the control group 144 ± 2 days. The mean birth weight of the cryosurgically treated group was 3.8 ± 0.8 kg and that of the control group was 3.4 ± 0.6 kg. No statistical differences between the groups were found.

Cardiac catheterization: *Cryosurgically treated group:* The 3-hour-old lamb had marked tachypnea and tachycardia. Right ventricular pressure was systemic (70 mm Hg) and the end-diastolic pressure ranged from 10 to 20 mm Hg. The aortogram demonstrated a large amount of left-to-right shunting through a widely patent DA. The 3-day-old lamb had a right ventricular pressure ranging from one third to one half systemic with a 40% left-to-right shunt. An aortogram demonstrated a patent DA.

The third lamb was catheterized 3 times. The first 2 catheterizations demonstrated pulmonary arterial pressure to be 80% of systemic and a 65% left-to-right shunt. The aortograms demonstrated a patent DA (Fig. 1). The third catheterization, at 93 days of age, demonstrated no DA shunting.

Control group: The 3-day-old lamb had no DA shunting. Necropsy confirmed closure of the DA.

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Pathologic findings: *Gross:* In the cryosurgically treated group (Fig. 2) the DA surface was irregular. The wall was thick and hard and on sectioning was gritty. No control animal had these characteristics. The DA was closed in all control lambs. In contrast, 4 animals in the cryosurgically treated group had a patent DA, except for the lamb whose DA was patent at catheterization on the 4th and 14th days of age (see foregoing) but closed at 93 days of age.

Microscopic study: Control group: The DA showed a regular parallel array of circular smooth muscle bundles separated by elastic fibers in the myxoid stroma (Fig. 3). No abnormalities or cellular "cushions" were seen in the intima. The lumen was seen only as a small elongated slit. Longitudinal smooth muscle bundles were irregularly located in the outer one third of the media.

Cryosurgical group: An extensive deposition of calcium, in the form of shards, granules, and irregular plates, was present in the outer one half to one third of the media (Fig. 4). Small foci of bland necrosis were occasionally seen. No evidence of acute inflammation was present. A sparse chronic inflammatory infiltrate, composed predominantly of lymphocytes, was seen in the periphery in 2 cases. In the areas of calcific deposits, a concomitant loss of elastic tissue was found without evidence of an increase in fibrous tissue. An absence or decrease of smooth muscle cells was noted in these areas of necrosis and calcification. Small cellular intimal cushions, composed of longitudinal bundles of smooth muscle cells, were seen as well, but these nodules or cushions did not compromise the lumen. In general, the DA lumen was widely patent, with the lumen averaging approximately one half of the total vessel diameter.

The 1 cryosurgically treated DA that was closed had its lumen filled differently from that of the control DA. Large protuberant intimal smooth muscle bundles appeared to block and distort the lumen into a slit (Fig. 5). Small deposits of fibrinous material were seen in the intima as well. Similar to the closed control DA, prom-

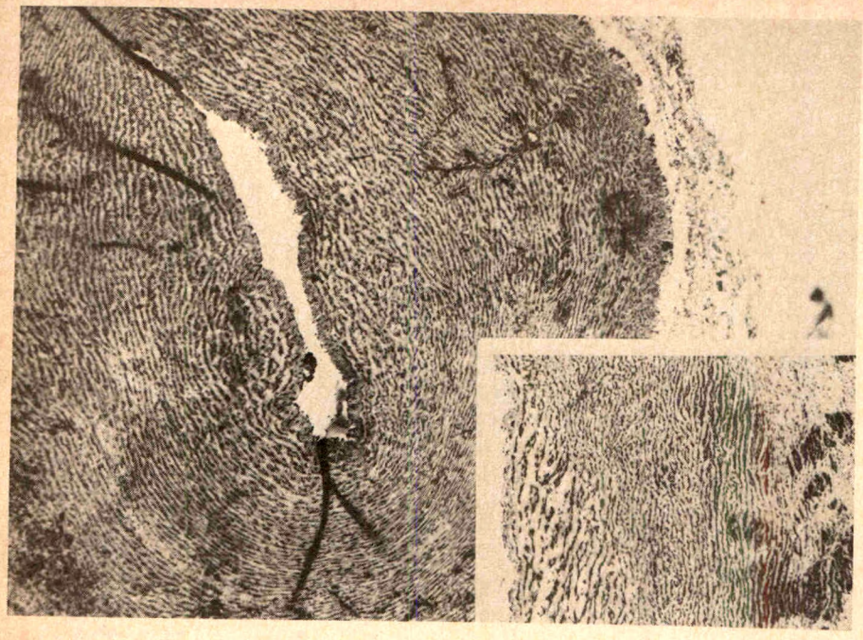

FIGURE 3. Normally closed ductus from a control lamb killed at 3 days of age. The lumen is a narrow slit. Regular parallel arrays of smooth muscle are separated by elastic fibers. Longitudinal bundles of smooth muscle are seen in the periphery of the vessel (**inset**). (Hematoxylin and eosin stain ×125, inset ×200, both reduced 54%.)

inent longitudinal smooth muscle bundles were seen in the outer media. Constriction did not appear to have played a major role in closure.

In 1 cryotreated DA, calcified degenerating adventitial ganglion cells were seen, but ganglia could not be identified in the other treated animals. A variable degree of proliferation of the adventitial small blood vessels was present. The 2 cryosurgically treated animals with the longest intervals between treatment and killing, 31 and 104 days, had an unusual histologic pattern. A marked foreign body giant cell reaction was present in the area of calcific deposits (Fig. 5). The disrupted calcified elastic fibers appeared to be the cause of the reaction.

Discussion

Closure of the DA after birth has been characterized as having 2 components: functional closure and anatomic closure.[9–12] Functional closure is related to constriction of the smooth muscle within the wall and thus obliteration of the lumen. A wide variety of vasoactive substances have been found to modulate this constriction—for example, the prostaglandins, bradykinin, acetylcholine, epinephrine, and norepinephrine.[13–16] In addition, the DA is well innervated with sympathetic nerves whose stimulation could lead to constriction.[15] The second component, anatomic closure, has been related to changes within the wall after constriction, to luminal fibrosis, and to an increase in size of the "inti-

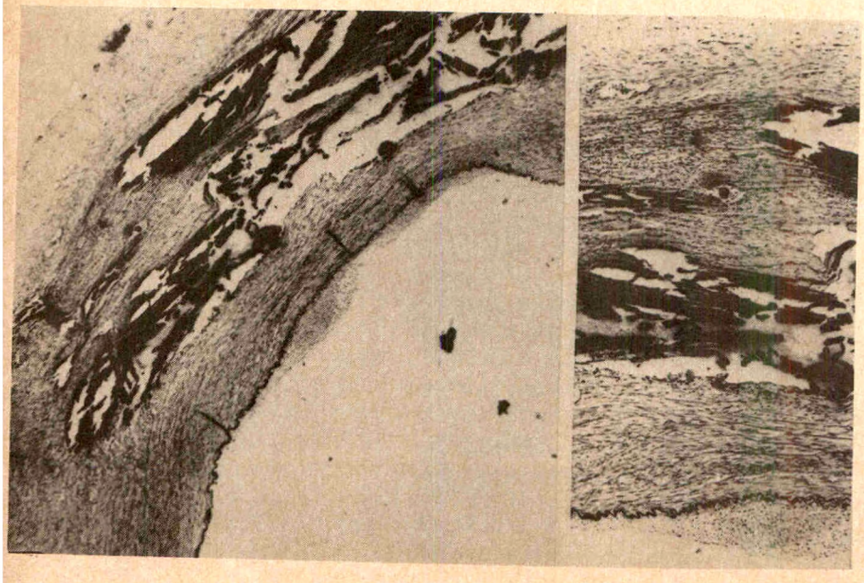

FIGURE 4. Ductus from a cryosurgically treated lamb killed at 6 hours of age. Prominent deposits of calcium are seen in the outer two thirds of the media. The elastic fibers are disrupted in the area of calcification, but no fibrosis is present. A small intimal cushion (**right, bottom**) is seen. No peripheral longitudinal smooth muscle bundles are present. Compare with Figure 3. (Verhoeff-van Gieson elastic stain, **left** ×125, **right** ×300, both reduced 54%.)

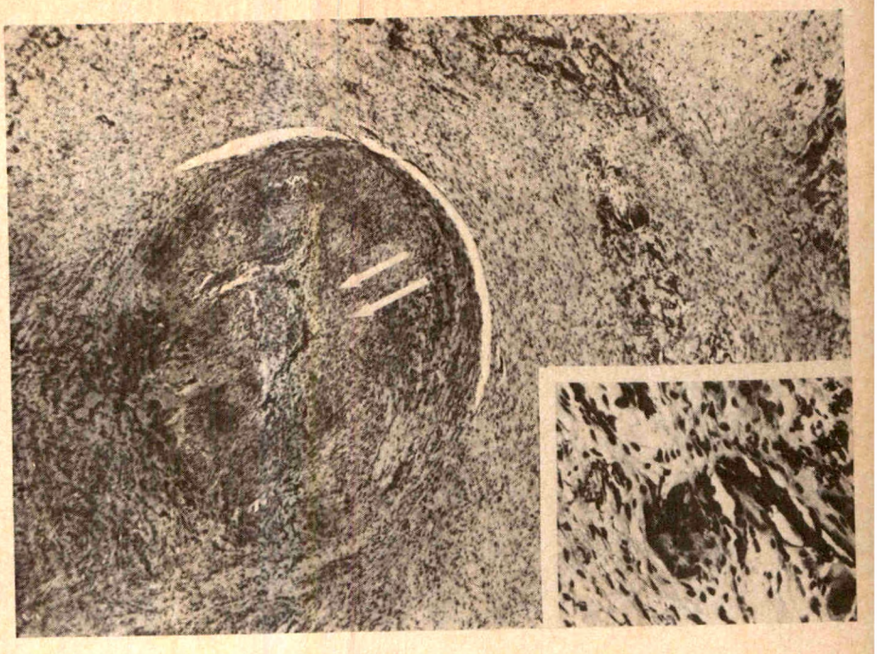

FIGURE 5. Ductus from the cryosurgically treated lamb whose ductus was open during the first 2 weeks of life, and closed by 93 days of age (see text). Calcification is seen as in Figure 4. In addition, the lumen is narrowed by prominent intimal cushions composed of longitudinal smooth muscle bundles (**area of double arrows**). In many areas the disrupted elastic fibers in the media have incited a foreign body giant cell reaction (**inset**). The **crescent-shaped clear area** is an artifact, the obliterated lumen is in the center of the longitudinal muscle bundles (**left of the arrowheads**). (Hematoxylin and eosin stain ×125; inset, Verhoeff-van Geison elastic stain ×350, both reduced 54%.)

mal cushions" that lead to luminal obliteration.[10–12] Because of the great clinical importance of DA patency in certain forms of congenital heart malformations, where closure may be a catastrophic event, approaches have been developed to interfere with these normal processes.[1–3] Formalin infiltration has been useful in interfering with closure, but it is not always successful.[1,4] In a group of 8 lambs that had formalin fetal DA infiltration and were examined after birth, 2 had only a probe patent DA. In humans formalin infiltration has been successful in maintaining DA patency, but in some DA narrowing occurs within weeks of the procedure and is associated with sudden clinical deterioration.[1]

Our decision to evaluate the effects of cryosurgery on normal neonatal DA closure was based in part on the successful and safe use of cryosurgery on other cardiovascular structures.[5–8] Freezing produces death of smooth muscle but does not harm fibrocytes so that a vessel is able to maintain its structure as a blood conduit.[5,6] The temperature of the DA can be lowered with a flat surface. Consequently, the treatment of the entire DA surface would be ultimately possible, whereas a formalin infiltrating needle cannot safely reach the posterior surface.

Fetal DA cryosurgical treatment was successful in preventing normal neonatal DA closure. In 1 lamb the DA closed by 3 months of age, but this lamb had a large left-to-right shunt during its first 2 catheterizations. One possible reason for this later closure is that the entire DA circumference could not be reached by the probe used in this study. This failure was evident in the histologic evaluation: the morphologic changes never extended beyond two thirds of the DA circumference.

Closure of this cryosurgically treated DA did not mimic that of the control group. Each control DA, obtained early in neonatal life, was marked by its constriction (Fig. 3). In contrast, this cryosurgically treated DA lumen was filled with smooth muscle cells located within the intima (compare Fig. 3 and 5). Intimal cushions of smooth muscle cells have been described as a normal human DA structure but were not present in our control group lambs.[10–12] In previous studies of normal DA closure, late obliteration occurred through luminal fibrosis and not through a proliferation of smooth muscle cells.[12] These differences suggest that the mechanisms for normal DA closure were not used in this cryosurgically treated DA.

The histologic effects of cryosurgical treatment of the DA differ from those described in dog carotid and femoral arteries and the rabbit descending aorta. In every cryosurgically treated DA, calcification was a prominent finding, but no increase in fibrous tissue was found. In contrast, fibrosis was a common finding in the dog and rabbit vessels, and calcification was rare in the dog and occurred weeks later in the rabbit. These differences could be related to the DA being treated at −60°C, whereas the other vessels appeared to have been treated at −180°C. Another potential explanation is that the younger the animal, the more likely that cold injury will produce calcific deposits: The dogs were adults, the rabbits were 3 months old, and our lambs were 115 to 135 days of gestation.

The cryosurgical treatment protocol used in this study was based on the protocol that successfully produced cicatrix formation in the dog myocardium.[6] When vessels have been subjected to lower temperature (−180°C) and longer periods of time (10 minutes), freezing of the vessel has occurred and wall-to-wall thrombosis has followed occasionally.[6] We hoped to avoid these complications with our protocol. DA occlusion with frozen blood is unlikely to have occurred because the area of frost extended only 1 to 1.5 mm

beyond the edge of the probe tip and all the lambs survived the surgery. At necropsy no evidence of thrombosis was found.

This study demonstrates that fetal DA cryosurgical treatment interferes with normal neonatal DA closure. Although the mechanisms through which freezing prevents closure are uncertain, a more complete treatment might further interfere with DA closure (for example, a probe can be made that will reach the DA posterior surface). The long-term effects of such cryosurgery on DA closure and the effects of neonatal cryosurgery remain to be assessed. Because of the devastating effects of a widely patent DA on the neonate with an otherwise normal circulation, such future studies might use a model in which the main pulmonary artery is partially or completely obstructed.

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Coronary Constriction by Leukotriene C_4, D_4, and E_4 In the Intact Pig Heart

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Leukotrienes are naturally occurring vasoactive metabolites of arachidonic acid that increase during inflammatory reactions and anaphylaxis. Coronary constriction and reduced myocardial contractility after leukotriene C_4 and D_4 administration were demonstrated in the isolated guinea pig heart. To explore the effects of leukotrienes in the in situ, blood-perfused heart, we administered leukotrienes C_4, D_4, and E_4 into the coronary artery of the domestic pig.

Increasing doses (0.1, 0.3, 1.0, and 3.0 μg) of leukotrienes C_4, D_4, and E_4 were injected into the left anterior descending coronary artery of 8 open-chest domestic pigs. Significant dose-related reduction in coronary blood flow was observed after each leukotriene administration. Three micrograms of each leukotriene produced the following maximal decreases (mean $\pm$ standard error): $C_4 = 80 \pm 9\%$, $p < 0.001$; $D_4 = 81 \pm 3\%$, $p < 0.001$; $E_4 = 64 \pm 12\%$, $p < 0.005$. In several instances, surface electrograms recorded from the myocardial region exposed to leukotrienes showed signs of focal myocardial ischemia, sometimes accompanied by ventricular arrhythmia. Significant elevation of left ventricular end-diastolic pressure was observed after large doses (1 or 3 μg) of leukotrienes C_4 and D_4. Minimal (5 to 10%) decreases in mean arterial pressure and no change in heart rate were observed after leukotriene injection.

We conclude that leukotrienes C_4, D_4, and E_4 are extremely potent coronary constrictors in the in situ heart. The intensity of response and associated electrocardiographic signs of ischemia suggest that constriction is mainly due to a primary effect on vascular smooth muscle. However, coronary flow reduction may also reflect consequences of a primary negative inotropic action. Leukotrienes may play a significant role in the pathogenesis of a variety of cardiac disorders, particularly those associated with extensive inflammatory changes.

Leukotrienes are a recently identified family of compounds whose potent biologic activity may figure significantly in disease processes. These naturally occurring metabolites of arachidonic acid are produced by lipoxygenase of white blood cells, mast cells, and other cell types. Their production is stimulated by a variety of pathologic circumstances including cell exposure to antigen-antibody complexes, activated complement, and other elements of the inflammatory response. Leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4) are potent constrictors of smooth muscle in several different preparations.[1–3] Because leukotrienes are major constituents of slow-reacting substance of anaphylaxis (SRS-A), a principal humoral mediator of adverse events in anaphylaxis, they may be responsible for coronary constriction that has been observed during anaphylactic reactions.[4,5] Vasoconstriction has been demonstrated by the capacity of LTC_4 and LTD_4 to increase systemic vascular resistance in the rat,[6,7] to reduce perfusion of guinea pig skin,[8] and to diminish coronary flow in the isolated, crystalloid-perfused guinea pig heart.[9–11] To explore the possibility that leukotrienes might reduce coronary perfusion in the

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intact animal, we measured the effects of intracoronary administration of LTC_4, LTD_4, and LTE_4 in the in situ, blood-perfused hearts of domestic pigs.

Methods

Eight domestic pigs of either sex, aged approximately 10 weeks and weighing 17 to 32 kg, were sedated with ketamine hydrochloride, 20 mg/kg intramuscularly, and anesthetized with pentobarbital sodium, 2 to 4 mg/kg/h intravenously. Animals were ventilated with a Harvard respirator modified to deliver 3 cm of water positive end-expiratory pressure. Ventilatory rate and inspired oxygen concentration were adjusted to maintain partial arterial oxygen pressure at 80 to 120 mm Hg and partial carbon dioxide pressure at 35 to 40 mm Hg. Hematocrit was 25 to 32% (normal for pigs of this age). Catheters filled with heparinized saline solution were placed in the jugular vein and internal mammary artery. The left ventricular cavity was catheterized through the carotid artery. Rectal temperature, mean arterial pressure, left ventricular pressure, and lead II of the standard electrocardiogram were monitored continuously. In addition, a surface electrogram was recorded from the region supplied by the distal left anterior descending coronary artery using a saline-soaked cotton wick electrode. Rectal temperature was maintained at 37.5 to 38.5°C by an external heating pad. A left thoracotomy was performed and the heart suspended in a pericardial cradle. A circumferential electromagnetic flow probe was placed around an exposed proximal portion of the left anterior descending artery and attached to a 501D Carolina square-wave flowmeter. A fine tygon catheter used to administer the leukotriene was introduced into the left anterior descending artery several millimeters distal to the flow probe.[12]

Pure synthetic LTC_4, LTD_4, and LTE_4 dissolved in distilled water (kindly provided by Joshua Rokach, PhD, Merck-Frosst, Dorval, P.Q., Canada) were obtained frozen on dry ice and stored at −70°C. Stock solutions (1 mg/ml) were diluted with heparinized 0.9% saline solution (vehicle). On each study day, leukotriene concentration in stock solutions was confirmed by spectrometry at 280 nm. Intracoronary injection of 0.1 ml leukotriene solution was followed by a 0.5 ml vehicle flush. The pH of all injected solutions was 7.15 to 7.20. After baseline recording of heart rate, mean arterial pressure, left ventricular pressure, and mean coronary blood flow, a 0.5 ml bolus of the vehicle was injected into the left anterior descending artery. Fifteen minutes later, individual bolus doses of leukotrienes were delivered within 3 seconds in ascending order: 0.1, 0.3, 1.0, and 3.0 μg. After each bolus, monitoring of all variables continued for 10 to 15 minutes or until return to baseline values, whichever was longer. The order of leukotriene administration was interchanged during successive studies and had no effect on the results. Animals were killed with additional pentobarbital sodium and potassium chloride. A paired data analysis using Student's *t* test was applied to evaluate leukotriene effects. Results are reported as mean ± standard error of the mean. Correlation between coronary blood flow and left ventricular end-diastolic pressure was tested by linear regression.

Results

Before leukotriene administration, mean coronary blood flow was 46 ± 5 ml/min. Table I shows the percent decrease in coronary blood flow after intracoronary injection of the leukotrienes. Each leukotriene caused significant reduction of coronary blood flow at the smallest dose tested. The maximal change in coronary blood flow after the smallest dose of LTC_4, LTD_4, and LTE_4 occurred 7 ± 2, 10 ± 2, and 9 ± 2 seconds, respectively, after leukotriene injection, and recovery to baseline level was completed within 2 to 3 minutes. Larger doses of each leukotriene produced profound, transient reduction in coronary blood flow. Total arrest of flow (coronary blood flow ≤1 ml/min) was observed after 9 such injections. The maximal change in coronary blood flow after the largest dose of LTC_4, LTD_4, and LTE_4 occurred 18 ± 2, 21 ± 4, and 8 ± 1 seconds, respectively, after the leukotriene injection, and recovery was completed within 3 to 4 minutes. Saline injection had no consistent effect on coronary blood flow, left ventricular end-diastolic pressure, mean arterial pressure, or heart rate.

TABLE I Percent Decrease in Mean Coronary Blood Flow After Intracoronary Injection of Leukotrienes

Dose (μg)	Leukotriene C_4 (n = 6)	D_4 (n = 8)	E_4 (n = 5)
0.1	32 ± 17	39 ± 5*	50 ± 5*
0.3	65 ± 3*	64 ± 9*	48 ± 8†
1.0	65 ± 14†	61 ± 10*	56 ± 8*
3.0	80 ± 9*	81 ± 3*	64 ± 12†

* $p < 0.001$.
† $p < 0.005$.

Table II represents the effects of intracoronary leukotriene administration on left ventricular end-diastolic pressure and mean arterial pressure. The reduction in coronary blood flow was not accompanied by significant changes in left ventricular end-diastolic pressure or mean arterial pressure after the smallest dose of leu-

TABLE II Left Ventricular End-Diastolic Pressure and Mean Arterial Pressure Before and After Intracoronary Injection of Leukotrienes

Dose (μg)	LVEDP (mm Hg) Base	LVEDP (mm Hg) LT	MAP (mm Hg) Base	MAP (mm Hg) LT
		LTC_4 (n = 6)		
0.1	7 ± 2	11 ± 3	90 ± 7	88 ± 5
0.3	9 ± 2	14 ± 3*	91 ± 5	89 ± 4
1.0	8 ± 1	12 ± 3	95 ± 5	90 ± 4
3.0	9 ± 1	14 ± 3†	98 ± 5	88 ± 4*
		LTD_4 (n = 8)		
0.1	9 ± 2	15 ± 3	89 ± 5	87 ± 5
0.3	8 ± 2	14 ± 2	92 ± 5	87 ± 5
1.0	9 ± 2	15 ± 3‡	99 ± 5	93 ± 4*
3.0	9 ± 2	16 ± 2*	96 ± 5	87 ± 3
		LTE_4 (n = 5)		
0.1	6 ± 1	8 ± 1	92 ± 6	89 ± 6
0.3	9 ± 2	12 ± 3	97 ± 4	94 ± 6
1.0	9 ± 3	10 ± 4	101 ± 7	93 ± 9‡
3.0	6 ± 2	11 ± 3	96 ± 5	90 ± 5‡

* $p < 0.005$.
† $p < 0.01$.
‡ $p < 0.025$.
Base = values measured immediately before leukotriene injection; LT = values measured at maximal coronary flow reduction after leukotriene injection; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure.

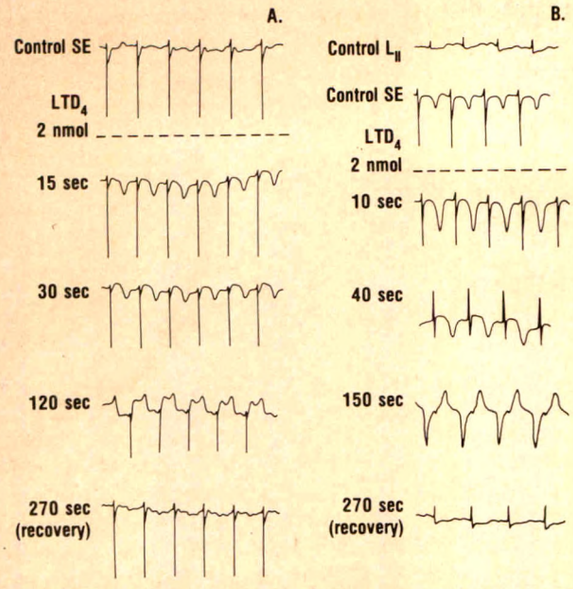

FIGURE 1. Focal electrocardiographic changes after intracoronary injection of 2 nmol (1 μg) of LTD_4. **A,** surface electrogram (SE) recorded from the region perfused by the left anterior descending coronary artery distal to the catheter entry site. Recordings were made before LTD_4 administration (control) and after administration at 15 seconds (T-wave inversion), 30 seconds (S-T elevation), 120 seconds (severe S-T elevation), and 270 seconds (recovery). **B,** the conventional lead II and SE are shown with normal sinus rhythm before LTD_4 administration, ischemic changes in SE 10 and 40 seconds after LTD_4 administration, and ventricular rhythm in SE after 150 seconds. Normal sinus rhythm in lead II was recorded after 270 seconds (recovery).

kotriene. After 1.0 and 3.0 μg of LTC_4 and LTD_4, a profound decrease in coronary blood flow was accompanied by a significant elevation in left ventricular end-diastolic pressure and a slight decrease (5 to 10%) in mean arterial pressure at the peak of leukotriene effect. Left ventricular end-diastolic pressure and mean arterial pressure returned to baseline along with recovery of the coronary blood flow. Mean heart rate (pretreatment range 135 to 145 beats/min) remained unchanged after all doses. Linear correlation analysis between the absolute change in coronary blood flow and the absolute change in left ventricular end-diastolic pressure showed no significant correlation.

Figure 1A illustrates signs of ischemia on the surface electrogram when coronary blood flow was reduced by 85% after 1 μg of LTD_4. The changes in T wave and S-T segment rapidly reversed on return of coronary blood flow to baseline. Similar changes occurred in 3 other pigs.

Transient rhythm disturbances were observed in 4 of 8 pigs given 1 or 3 μg of LTC_4 or LTD_4. All arrhythmias were ventricular in origin, occurred immediately after peak hemodynamic effects, and disappeared 3 to 5 minutes later.

Discussion

Our results demonstrate that LTC_4, LTD_4, and LTE_4 each produced a dose-related decrease in coronary blood flow when administered as a bolus into the coronary artery of the pig. Associated hemodynamic findings, particularly at smaller doses, suggest that coronary blood flow decreased in response to a leukotriene-induced increase in coronary vascular resistance rather than a decline in driving pressure across the coronary bed or diminution in duration of diastolic coronary flow. These data support previous results demonstrating leukotriene-mediated vasoconstriction in isolated, crystalloid-perfused hearts.[9–11] One report describes similar results in the in situ sheep heart.[13] The attendant electrocardiographic evidence of local myocardial ischemia in our preparation and the severity of flow decrement imply that coronary constriction was a primary response to leukotrienes rather than a secondary response to reduced myocardial perfusion requirements.

Intracoronary administration of leukotrienes tended to limit effects to a single region of myocardium as well as to maximize direct action of a given dose on coronary flow. The S-T segment elevation and deep symmetrical T-wave inversion in the locally recorded electrocardiogram, the development of ventricular ectopy, the decrease in mean arterial pressure, and the increase in left ventricular end-diastolic pressure transiently occurring with administration of larger doses of the leukotrienes may all be explained as the electrical and mechanical consequences of regional ischemia. Reduction in mean arterial pressure is likely to represent a response to myocardial ischemia rather than a direct action of leukotrienes on the systemic circulation, because intravenous leukotriene administration consistently produces early pressor responses in the rat and guinea pig.[6–8] However, data from isolated hearts suggest a direct toxic influence on mechanical properties of myocardium.[10] In our study the increase in left ventricular end-diastolic pressure was not correlated with the decrease in coronary flow, possibly reflecting negative inotropic effects of leukotrienes not mediated by reduced myocardial perfusion. In some instances, a primary negative inotropic action might contribute to coronary constriction through autoregulatory mechanisms.

The capacity of leukotrienes to reduce coronary flow and cause electrical and mechanical myocardial dysfunction suggests that leukotrienes may play a significant role in the pathogenesis of a variety of cardiac disorders, particularly those associated with extensive release of SRS-A. For example, anaphylaxis is associated with contractile depression, arrhythmias, reduced coronary flow, and abundant release of SRS-A.[14,15] Immune complexes can cause the heart to release large quantities of SRS-A, demonstrating the capacity of cardiac tissues to produce leukotrienes in abundance when stimulated appropriately. Because leukotrienes can produce such extreme reduction in coronary flow, even in subnanomole quantities, the cardiac abnormalities known to accompany anaphylaxis may reflect myocardial ischemia due to leukotriene action as well as the effects of histamine and other vasoactive or cardiodepressor factors.[14,15]

Leukotrienes may exert a much broader influence in the pathogenesis of cardiac disorders. Because leukotrienes are produced by inflammatory cells from ubiq-

uitous constituents, their potent coronary constrictor activity constitutes a novel and potentially important link between inflammatory processes and increased coronary vascular resistance. Coronary vessel tone may be an important factor in the precipitation and perpetuation of ischemic events with variant angina, unstable angina, and acute myocardial infarction.[16] Local or systemic release of leukotrienes in response to tissue injury might contribute significantly to coronary spasm, stasis of flow, and intravascular thrombosis. Thrombus-promoting action may be potentiated by leukotriene-induced release of thromboxane A_2.[17] LTC_4 and LTD_4 also promote tissue edema[18] that may further diminish coronary perfusion and augment cellular injury. Leukotriene-induced coronary constriction may add significantly to a mechanical plugging effect of white blood cells in ischemic myocardium.[19] Under these circumstances, the use of specific antagonists of leukotriene may offer a significant and possibly synergistic therapeutic modality.

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The AJC in May 1958

CAROLE A. WARNES, MB, BS, MRCP and WILLIAM C. ROBERTS, MD

This is the first of a new section in the *Journal* which will examine 1 or more articles published in the same month's issue 25 years ago. In contrast to a recent issue (February 1983), the May 1958 AJC was shorter in length, each page was less compact, and each paper was less concise and scientific (Table I). Not a single 1 of the 17 articles in the May 1958 issue contained a p value! Three articles in the May 1958 issue have been selected for comment.

Aortic Stenosis (Paul Wood)

In an 18-page lead article Paul Wood, from London, described clinical features in 250 patients with aortic stenosis (AS) he had seen in a 7-year period. During the same period, he saw 78 patients with "pure rheumatic aortic regurgitation" (AR) and "about 700" with mitral valve disease. In this study Wood excluded patients with "dominant mitral valve disease." The cause of AS in his 250 patients was considered rheumatic in 180, congenital in 54, and unstated in 16. The ages of the 180 rheumatic AS patients ranged from 19 to 79 years (average 46), and 44% had a history of a "rheumatic state." In >90% the degree of AS was considered "severe." Calcific deposits in the aortic valve were observed by radiography in 80% of the patients >30 years of age. The male to female ratio was 2 to 1. Of those patients with any symptoms, angina pectoris was present in 70%, syncope in 33%, and breathlessness in 45%. Wood carefully documented the physical signs of AS, and these observations remain valid. Aortic valvotomy was performed in 80 patients with a 20% mortality: 54% had a good result and 26% an "indifferent" result. Wood wrote: "In conclusion one might say that at the present time aortic valvotomy is too hazardous and too crude an operation to advise it when it is most desirable (just before the onset of symptoms) and frequently too late when impending disaster makes it imperative; nevertheless, the results of skilled surgical treatment far outweighs anything that medicine has to offer."

TABLE I Comparison of 2 Issues of AJC: May 1958 and February 1983

Item	May 1958	February 1983
Number of pages	121	262
Number of lines per column	50	62
Number of letter spaces per line	46	55
Number of papers	17	47
Average number of pages per paper	7	6
Average number of authors per paper	2	5
Maximum number of authors on a paper	5	18
Average number of references per paper	14	22
Number of papers from outside the U.S.	1 (7%)	9 (19%)
Number of papers containing a p value	0	23 (49%)

This study subsequently has been referred to on many occasions. All 250 patients with AS were studied personally by Wood. Despite the excellence of his description of the clinical signs, the paper, in retrospect, has certain deficiencies. His discussion on the etiology of AS appears to have been based entirely on historic information. It is now clear that, for practical purposes, AS has only 3 etiologies: congenital, rheumatic, and degenerative. Although Wood mentioned the congenital and rheumatic etiologies, the criteria for inclusion in either category were not defined. Wood thus adhered to the thinking of the time, that is, that rheumatic heart disease was the major cause of AS and AR, a viewpoint popularized by Karsner and Koletsky. The bicuspid aortic valve was not mentioned in his report, yet today we know that most patients age ≤65 years with AS (with or without AR) unassociated with mitral valve disease have the AS superimposed or a congenitally bicuspid aortic valve. The degenerative or wear-and-tear etiologic concept of AS, likewise, was not considered in 1958. Irrespective of its limitations, this single-authored paper remains a classic on the subject.

Idiopathic Dilated Cardiomyopathy (David H. Spodick* and David Littman)

Spodick and Littman from West Roxbury, Massachusetts, summarized clinical observations in 8 patients with what we now call "idiopathic dilated cardiomyopathy." The 8 patients were seen at a Veterans Administration Hospital during a 9-year period. In their discussion, they mentioned that a "search of the world literature" disclosed 72 reported patients with the iso-

* Currently a member of the AJC's editorial board.

lated finding of "unexplained large heart." This study is a fine review of reported patients with presumed idiopathic dilated cardiomyopathy up to 1958.

Coronary Heart Disease: An Evaluation and Criticism of Present-Day Concepts (Claude S. Beck)

This 6-page editorial by a pioneer of coronary surgery criticizes the complacency of cardiologists for not considering surgery the most definitive form of therapy for this condition. Beck described 4 surgical procedures which might increase myocardial oxygenation: "abrasion of surface of heart and lining of parietal pericardium, a light application of 5% aqueous solution of trichloroacetic acid to the surface of the heart between the coronary arteries, a light sprinkling of powdered asbestos on the surface of the heart, narrowing the coronary sinus to a diameter of 3 mm, application of parietal pericardium and its outside fat to the surface of the heart as a graft." The concept of coronary bypass grafting was mentioned briefly: "We tried to add blood from grafts on the heart including the mammary arteries. We also tried to clean out the coronary arteries and also to place shunts in them. Others are working on these developments. Perhaps something more effective will be developed in the future and this work should be encouraged."

Beck wrote, "The definition of progress is the replacement of wrong ideas by scientific facts . . . . Every age, including our own, knows so much that isn't so."

Program of the College Annual Meeting

The May 1958 issue also included (in 5 pages) the entire program of that year's annual meeting of the American College of Cardiology.

Kent Pathways Visualized in Situ and Removed at Operation

Richard Brodman, MD
John Fisher, MD
Sumi Mitsudo, MD
Soo Gyum Kim, MD
Jeffrey Matos, MD

In 2 patients, left free wall accessory atrioventricular muscle bundles (Kent bundles) were visualized in situ during dissection of the coronary sulcus fat and removed for histologic documentation. Kent pathways, therefore, may be visible if looked for at operation.

There is substantial evidence that the structures removed were Kent pathways: (1) they were found in the location predicted by careful pre- and intraoperative mapping (Fig. 1 and 2); (2) they bridged the atrium and ventricle (Fig. 3 and 4); (3) they consisted of muscle fibers surrounded by epicardial fat (Fig. 5 to 8); and (4) electrophysiologic testing confirmed division of the Kent pathways. Sealy et al[1] found in their review that only 5 of the 21 postmortem specimens had more than 1 strand. The presence of other smaller muscle bundles cannot be excluded as they may have been divided before visualization with the 2.5 power operating loops.

The variable location and number of Kent pathways in the epicardial fat and the sheer presence of fat in the

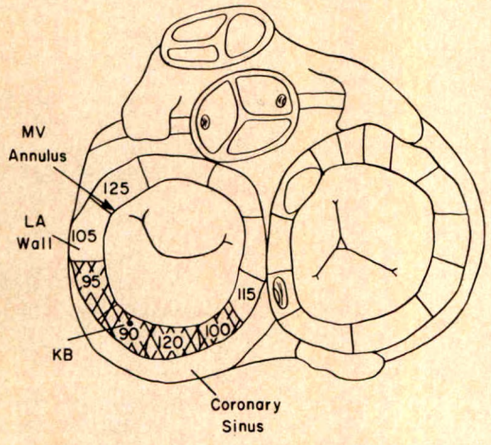

FIGURE 1. Intraoperative left atrial (LA) epicardial map generated before excision of the anomalous pathway in Case 1. Conduction times are in milliseconds after ventricular pacing impulse. KB represents the site of the anomalous pathway visualized at surgery, and the **cross-hatched area** represents the extent of operative dissection of coronary sulcus fat. MV = mitral valve.

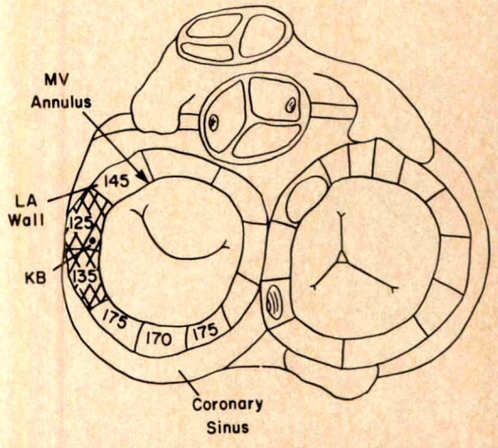

FIGURE 2. Intraoperative left atrial (LA) epicardial map generated before excision of the anomalous pathway in Case 2. Conduction times are in milliseconds after ventricular pacing impulse. KB represents the site of the anomalous pathway visualized at surgery, and the **cross-hatched area** represents the extent of operative dissection. MV = mitral valve.

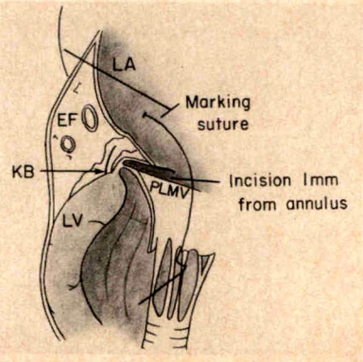

FIGURE 3. Relation of the anomalous pathway (KB) found at surgery to the marking suture, epicardial fat (EF), and atriotomy made just above the anulus of the mitral valve (PLMV) in Case 1. LA = left atrium; LV = left ventricle.

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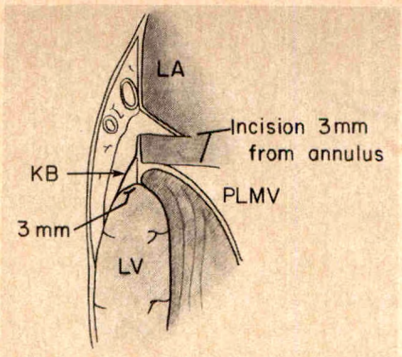

FIGURE 4. Relation of the anomalous pathway (KB) removed at surgery to the atriotomy and mitral anulus in Case 2. Abbreviations as in Figure 3.

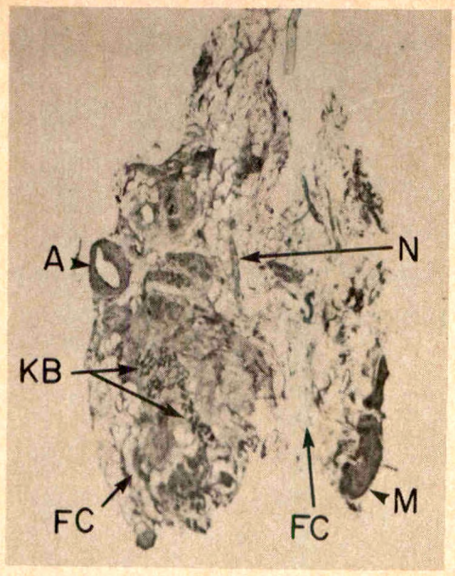

FIGURE 5. Biopsy specimen of tissue removed from the coronary sulcus in Case 1 containing Kent fibers (KB), fat cells (FC), nerve fibers (N), artery (A), and myocardial fibers of left atrium (M). (Hematoxylin and eosin stain; magnification ×25.)

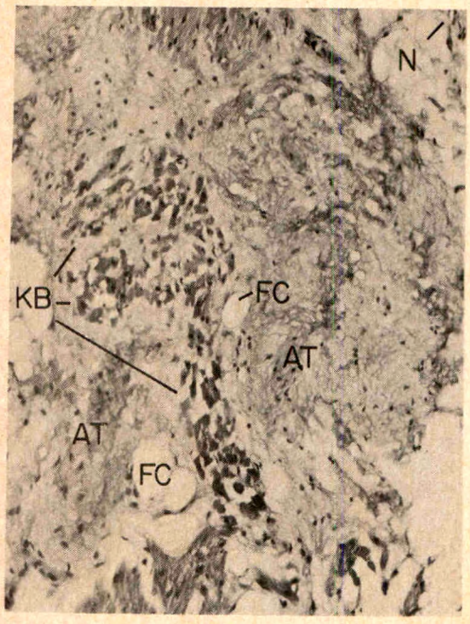

FIGURE 6. Higher power photomicrograph of the Kent fibers (KB) from Case 1 surrounded by fibroadipose tissue (AT and FC) containing nerve fibers (N). (Magnification ×100, reduced 28%.)

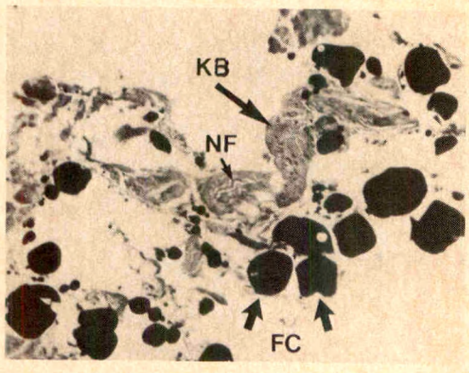

FIGURE 7. Biopsy specimen of tissue removed from the coronary sulcus in Case 2 containing Kent fibers (KB), fat cells (FC), and possibly a nerve fiber (NF). The fat cells are black because this specimen was fixed in glutaraldehyde, postfixed in osmium tetroxide, and then stained with hematoxylin and eosin. (Magnification ×100, reduced 45%.)

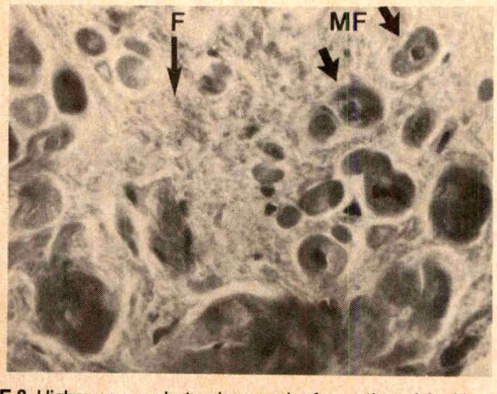

FIGURE 8. Higher power photomicrograph of a portion of the Kent fibers seen in Figure 7, showing marked fibrosis of muscle fibers (F) interspersed with normal muscle fibers (MF). (Magnification × 400, reduced 40%.)

coronary sulcus may make identification difficult. It should, however, be possible to identify a structure with an average widest dimension of 1.8 mm,[1] particularly if magnification currently available in the operating room is used.

Unless these cases prove atypical, the Kent pathway will become visible and divisible, not invisible and divisible. Although visual identification of the bundle of Kent is not a necessary part of the operative procedure for Wolff-Parkinson-White syndrome, removal of a visible bundle of Kent may make in vitro electrophysiologic study possible.

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Lipoma of the Mitral Valve and Papillary Muscle

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Gordon Williams, MB, MRCP
Leon Gerlis, FRC (Path)
Duncan Walker, MB, FRCS
Olive Scott, MD, FRCP

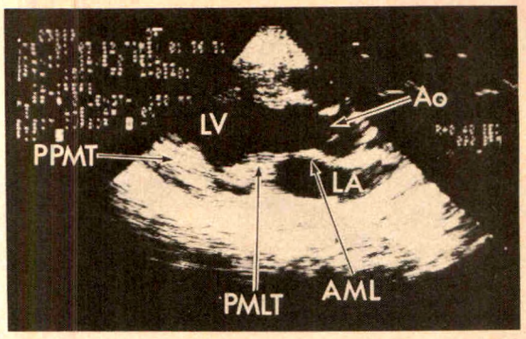

FIGURE 2. Long-axis 2-dimensional echocardiogram of the left ventricle. Two tumor masses are seen, 1 in the posterior mitral leaflet (PMLT) and the other in the posterior papillary muscle (PPMT). AML = anterior mitral leaflet; Ao = aortic root; LA = left atrium; LV = left ventricle.

Mitral valve tumors are rare. This report describes findings in a patient with mitral regurgitation (MR) due to multiple mitral valve lipomas.

An asymptomatic girl presented at age 2 years with signs of MR. The electrocardiogram showed left ventricular (LV) hypertrophy, and a chest radiogram showed an enlarged left atrium but was otherwise normal. At 4 years, cardiac catheterization showed a mean pulmonary capillary wedge pressure of 14 mm Hg with a V wave of 27 mm Hg. The LV cineangiocardiogram showed free MR. No filling defect was seen in the left ventricle, left atrium, or region of the mitral valve. The patient remained asymptomatic; hemoglobin, white blood cell count, and erythrocyte sedimentation rate were normal.

Echocardiography, performed when the patient was 14 years of age with a mechanical sector scanner (Advanced Technical Laboratories, Seattle, Washington, 5 MHz probe), showed a dense mass of echoes arising from the posterior mitral leaflet; it extended anteriorly toward the free edge of the anterior leaflet, from which it was separated by an echo-free space (Fig. 1). The 2-dimensional echocardiogram revealed the presence of 2 tumors, 1 in the posterior mitral leaflet and 1 in the posterior papillary muscle (Fig. 2).

The mitral valve was explored when the patient was 16 years old. The posterior cusp was replaced by a hemispher-

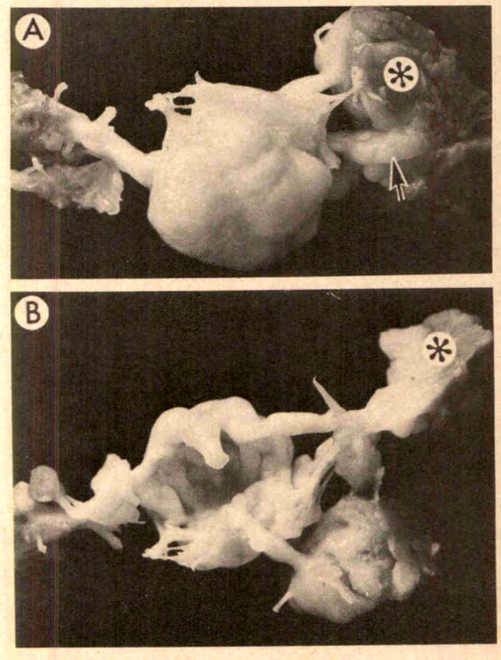

FIGURE 3. A, excised posterior mitral valve cusp, viewed from the atrial aspect, showing the globular tumor replacing most of the free portion. The **asterisk** indicates tumor involvement of a papillary muscle. The **arrow** indicates tumor spread upward into a chorda tendineae. **B,** concave ventricular aspect of the specimen.

From the Department of Paediatric Cardiology, Killingbeck Hospital, Leeds, England. This study was supported by the National Heart Research Fund, England. Manuscript received October 18, 1982; revised manuscript received and accepted December 15, 1982.

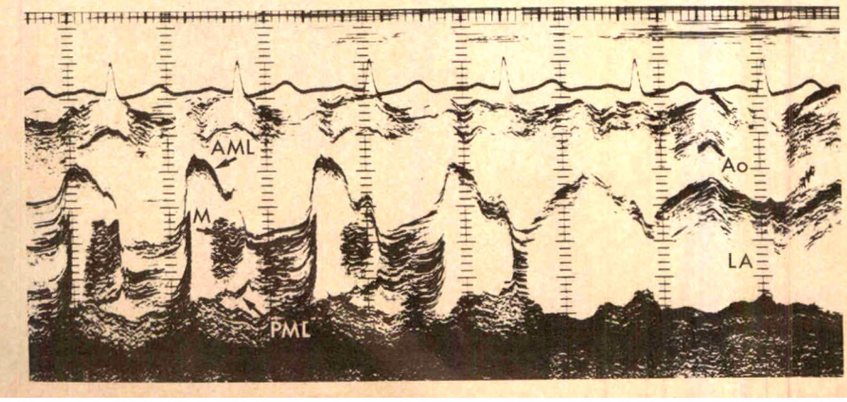

FIGURE 1. M-mode echocardiogram from the left ventricle (LV) to the aorta (Ao). A dense mass of echoes (M) arises from the posterior mitral leaflet (PML). The left atrial cavity (LA) is free of echoes.

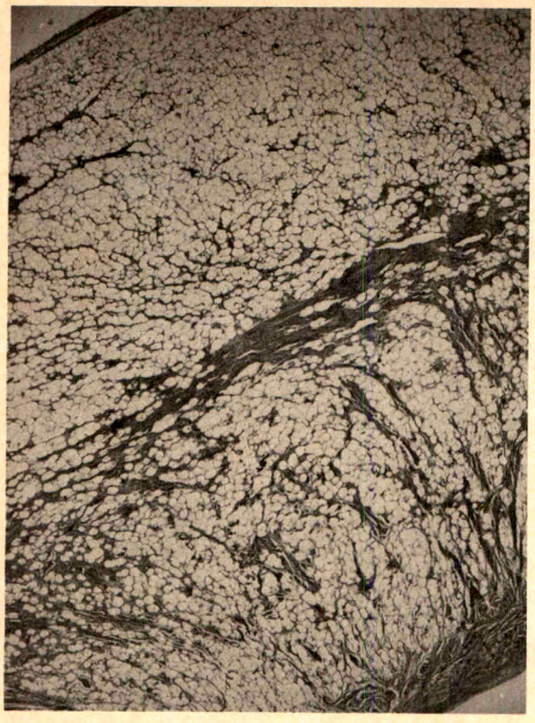

FIGURE 4. Histologic section of the valve tumor showing the mature fat cells. (Masson's trichrome stain; magnification ×25, reduced 13%.)

ical lobulated sessile yellow mass, 23 × 22 × 14 mm. The chordae tendineae of this cusp were thickened and emerged from another yellow 20 × 12 × 8 mm mass that had largely replaced the posterior papillary muscle (Fig. 3). The anterior cusp was normal. The mitral valve and the papillary muscles were excised and replaced by a 31 mm Björk-Shiley prosthesis. The postoperative course was uneventful. Histologic examination of sections of the valve and the papillary muscle tumors showed simple pure lipomas composed of mature fat cells (Fig. 4).

Valve lipomas are exceedingly rare. Two cases of lipoma involved the septal leaflet of the tricuspid valve.[1,2] Only 1 case of fibrolipoma of the mitral valve has been reported.[3] The present case is the first "pure lipoma" of the mitral valve to be reported. The M-mode echocardiogram disclosed the tumor in the posterior mitral leaflet but failed to identify the tumor in the posterior papillary muscle. Two-dimensional echocardiography showed both masses and provided better appreciation of their size, shape, location, and mobility.

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Massive Right Ventricular Outflow Tract Aneurysm After Ventriculotomy for Subvalvular Pulmonic Stenosis Associated With Peripheral Pulmonary Arterial Stenoses

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Charles L. McIntosh, MD, PhD
William C. Roberts, MD

Aneurysms that develop at sites of cardiac ventriculotomy incisions are recognized but infrequent consequences of such procedures.[1] Their development appears to be dependent on 2 major factors: (1) the peak systolic pressure within the ventricle after the incision, and (2) the length of the incision. The incidence of postventriculotomy aneurysm is far greater in the left ventricle than in the right because of the differences in peak pressures in each chamber. Herein, we describe a patient with *both* subvalvular pulmonic stenosis and peripheral pulmonary arterial stenoses in whom a massive right ventricular (RV) outflow tract aneurysm developed after operative relief of the subvalvular obstruction.

A 30-year-old woman (CC #05-28-81) had a precordial murmur at birth and cyanosis and clubbing of the digits by age 7 years. Results of 4 cardiac catheterization studies, summarized in Table I, confirmed the presence of subpulmonic obstruction, peripheral pulmonary arterial stenoses,

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TABLE I Hemodynamic Data

	Age (yr)			
Pressures (mm Hg)	8	15	Intra-operative	(6 mo PO) 16
Pulmonary artery (s/d)	100/	75/5	115/20	120/60
Right ventricle (s/d)	175/	180/7	120/20	120/16
RV inflow-outflow peak systolic gradient	75	105	5	0
Systemic artery (s/d)	. . .	110/60	120/60	120/70

PO = postoperative; s/d = peak systole/end-diastole.

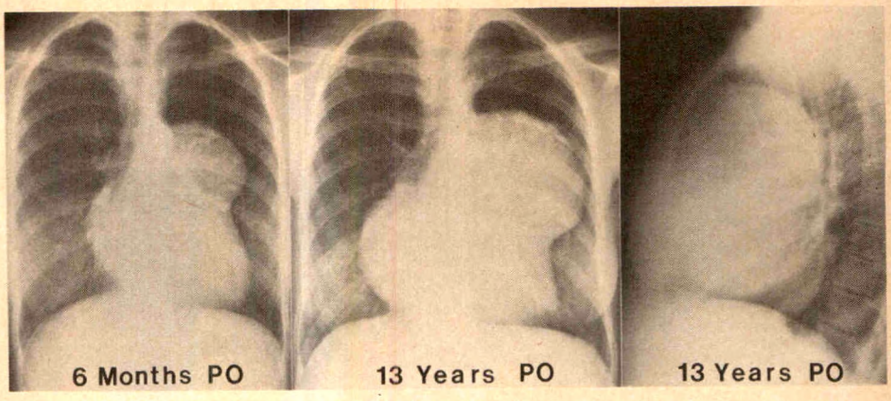

FIGURE 1. Radiographs of the chest 6 months and 13 years after operation, illustrating the development of the RV outflow tract aneurysm. A thin rim of calcium lines the wall of the aneurysm. PO = postoperative.

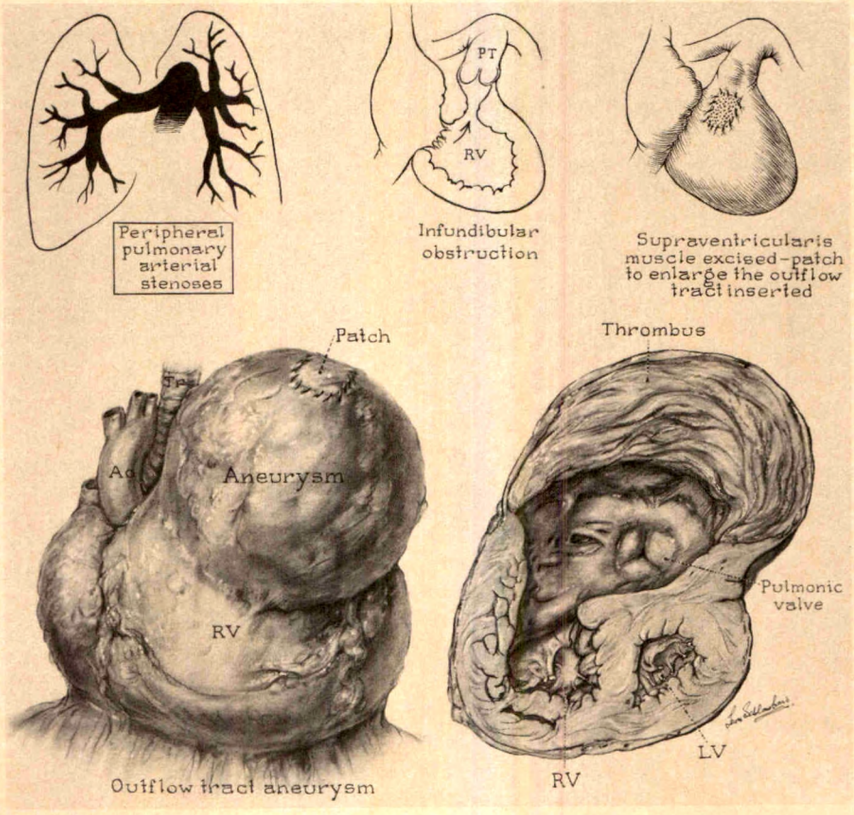

FIGURE 2. Diagrams illustrating various components of peripheral pulmonary arterial stenoses and RV infundibular obstruction, and the consequences of the right ventriculotomy. Ao = aorta; LV = left ventricle; PT = pulmonary trunk; RV = right ventricle.

and a right-to-left shunt through a patent foramen ovale. Syncope occurred at age 12 years, and by age 15 had become frequent and severe. The subpulmonic stenosis was operatively relieved at age 15 years by excision of portions of crista supraventricularis myocardium. A Teflon® fabric patch was used to enlarge the RV outflow tract. The patent foramen ovale was sutured closed.

Six months after operation, a pulsatile mass was present at the upper left sternal border of the heart (Fig. 1). During the next 13 years, the patient had no physical limitations and received no medications (functionally class I). She died suddenly at age 30 years after a febrile illness with hemoptysis.

At necropsy, the heart with the aneurysm weighed 830 g (Fig. 2 and 3). The RV outflow incisional aneurysm was partially filled with laminated thrombus and lined by focally calcified fibrous tissue. The aneurysm partially compressed the pulmonary trunk, left atrium, and left anterior descending coronary artery.

RV aneurysms of the magnitude described in this patient, to our knowledge, have not been described previously after right ventriculotomy. In this case, inoperable peripheral

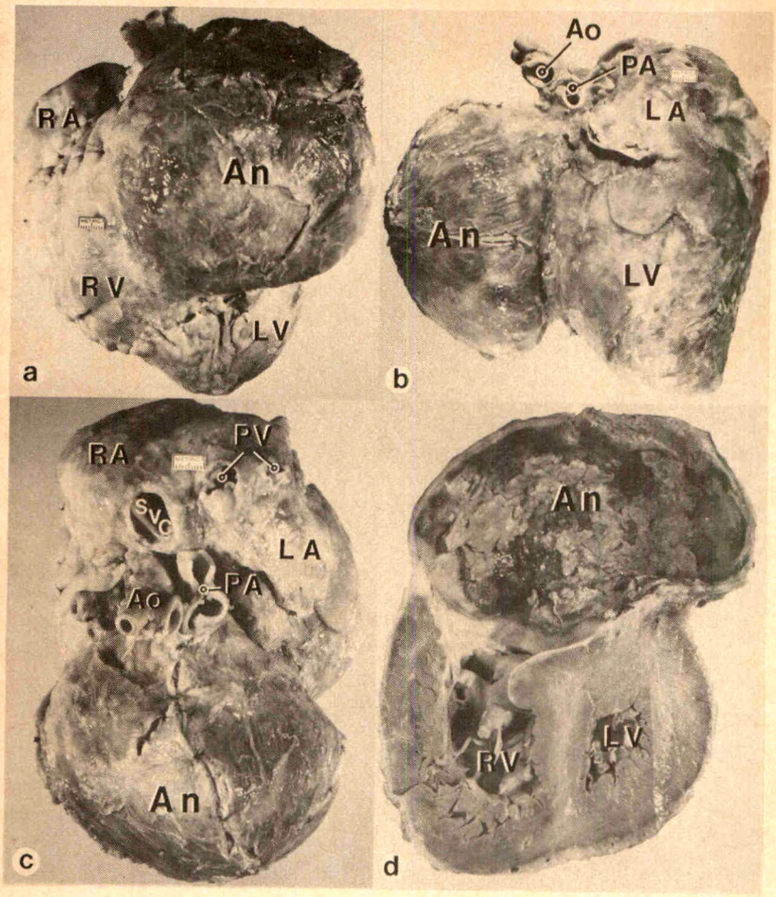

FIGURE 3. Photographs of the heart at necropsy including views of the anterior (**a**), left lateral (**b**), basal (**c**), and transverse cut (**d**) surfaces. The transverse cut illustrates the massive size of the aneurysm (thrombus removed) and the marked RV hypertropy. An = aneurysm; Ao = aorta; LA = left atrium; LV = left ventricle; PA = pulmonary artery; PV = pulmonary veins; RA = right atrium; SVC = superior vena cava. (Photographs by M. M. M. Moore.)

pulmonary arterial stenoses caused persistent, severe elevation of the RV systolic pressure, which in turn caused massive aneurysmal dilatation of the surgically incised RV outflow tract.

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Progressive Pulmonary Arterial Stenosis

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Gordon M. Folger, Jr., MD

Pulmonary arterial stenoses (PAS) are generally considered stable or nonprogressive malformations conforming to 1 of several anatomic configurations.[1] Documentation of progression in stenosis both anatomically and hemodynamically[2–5] has been rare, but such was the case in a patient we studied.

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TABLE I Comparative Hemodynamic Data

Site	4.5 Months Pressure (mm Hg)	4.5 Months Oxygen Saturation (%)	45 Months Pressure (mm Hg)	45 Months Oxygen Saturation (%)
RA	m 1	65	m 5	44
RV	45/3	63	128/8	46
PT	42/5 (m 22)	60	126/62 (m 72)	44
LPA	20/0 (m 15)	...	...	...
RPA	23/10 (m 1)	61	...	...
LA	m 1	85	m 3	70
LV	...	...	112/10	79

LA = left atrium; LPA = left pulmonary artery; LV = left ventricle; m = mean; PT = pulmonary trunk; RA = right atrium; RPA = right pulmonary artery; RV = right ventricle.

A 45 month-old girl was obtunded, retarded, and in severe right-sided heart failure when first seen. Multiple congenital anomalies including PAS had been diagnosed at age 4.5 months (Table I, Fig. 1). The height and weight were average

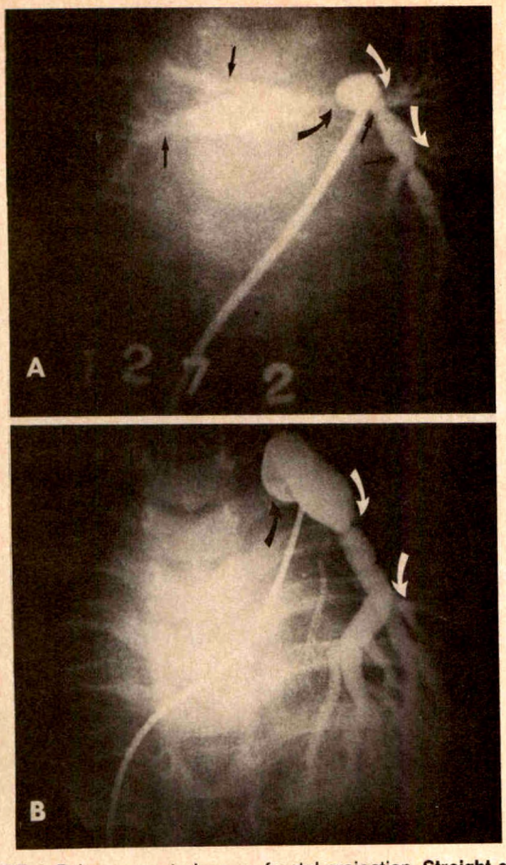

FIGURE 1. Pulmonary arteriogram, frontal projection. **Straight arrows** indicate major areas of stenosis; **curved arrows** denote those areas which may be identified as having progressed to total occlusion. **A,** 4.5 months of age; **B,** 45 months of age. Note the enlargement of vessels to the left lower lobe, resulting from near-total pulmonary blood flow to this area.

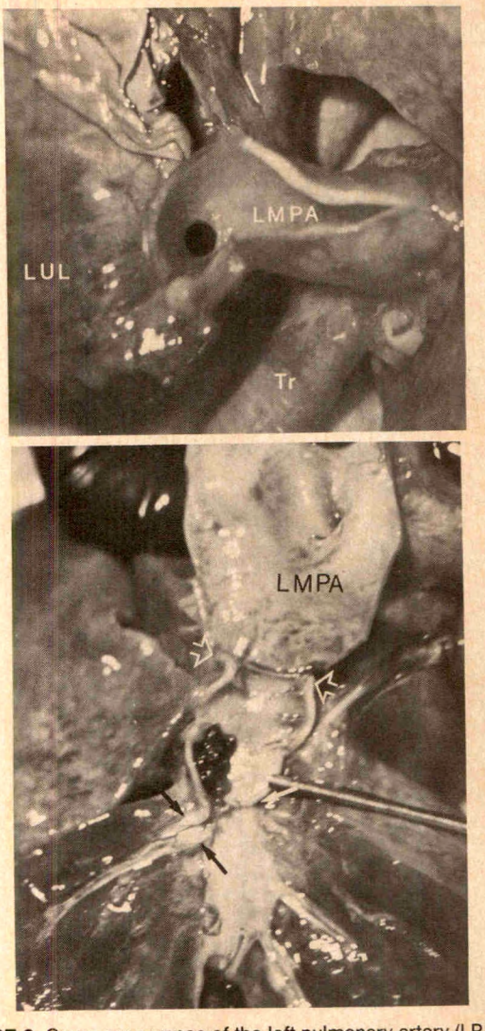

FIGURE 2. Gross appearance of the left pulmonary artery (LPA). **Top panel,** close-up of the left main pulmonary artery (LMPA) exposing first stenotic area just proximal to the left upper lobe (LUL) branch. The lesion is concentric, and its edges are smooth. **Bottom panel,** view of the entire left pulmonary artery. **Open arrows** indicate stenosis seen in the top panel; **solid arrows** indicate stenoses seen angiographically (see Fig. 1). Tr = trachea.

for a child of 12 months of age. She had coarse facial features, posteriorly positioned low-set ears, a bifid uvula, and hydrocephalus (treated earlier by ventriculoperitoneal shunt). Deep cyanosis and the murmurs of tricuspid and pulmonic valvular regurgitation were present.

Repeat cardiac catheterization (Table I, Fig. 1) disclosed more severe PAS with suprasystemic main pulmonary arterial systolic pressure and a large right-to-left shunt through the atrial septum. She died 8 days after this study.

At necropsy, multiple "shelf-like" projections involved both the major and the peripheral pulmonary arteries (Fig. 2). The pulmonary trunk was spared. Microscopically, the obstructing lesions were composed of discrete excrescences of hypertrophic media having an otherwise normal appearance.

PAS of a degree sufficient to produce systemic or suprasystemic systolic right ventricular and pulmonary arterial pressures is well recognized.[6] Progression of PAS, to the contrary, has been reported in only 4 patients[2–5] in whom the condition was isolated. Our patient is the only individual with hemodynamic documentation of progression substantiated by serial angiographic evaluation and confirmed by necropsy.

The cause of the progression in severity was not determined. It was clear, however, that thromboembolism was not a contributing factor. The relation of this child's obvious multiple anomalies with the PAS suggests a singular origin for the malformations.

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LETTERS*

HOLTER VERSUS ELECTROPHYSIOLOGIC STUDIES IN THE MANAGEMENT OF MALIGNANT VENTRICULAR ARRHYTHMIAS

We read with gratitude the report of the experience of Graboys et al[1] in treating patients with malignant ventricular arrhythmias with antiarrhythmic drugs. These observations by a very experienced group are an important landmark in the search for methods for managing patients at high risk of death due to arrhythmias. We will comment briefly on the study in general and then argue with 2 points made by these investigators: (1) the method is simple, inexpensive, and therefore easy to apply; and (2) the method is preferable to electrophysiologic guided treatment.

Graboys et al conducted an observational study, not an experimental one. Their patients are highly selected so that their sample is subject to biases that hamper inferences and extrapolation of the results to other institutions and patient groups. The 2 subgroups that are compared, that is, those that respond to antiarrhythmic treatment and those that do not, are not well characterized at baseline with respect to presence and extent of coronary artery lesions or left ventricular dysfunction. The authors state that left ventricular function is not different in the treatment responders and nonresponders. However, the left ventricular dysfunction data are weak on 3 counts: (1) only 64% of the patients had any measure of left ventricular dysfunction; (2) 3 different methods were used to estimate the ejection fraction (echocardiography in 37% of the cases); and (3) the ejection fraction cutpoint used for left ventricular dysfunction (that is, 50%) was too high. Because of these problems the misclassification rate is likely to be high. The assessment of left ventricular dysfunction would have been better if all patients had had radionuclide ventriculography to estimate the ejection fraction and if a cutpoint of 30 or 35% had been used. Because of these problems in evaluating left ventricular dysfunction, differences at baseline could account for differences in outcome. Also, there was no randomization or systematic assignment to alternative treatment regimens. Very little information was given on drug sequencing and selection. What were the 3 or 4 most common drug combinations and what was the prevalence of digitalis use? Which regimens most frequently caused adverse effects during a year of follow-up? How were changes to new treatments managed? We do not learn much from this report about the comparative worth of treatments. Nevertheless, these flaws are tolerable considering the state of knowledge in this field and the hypothesis that the authors wanted to test, although we will have to await confirmatory observational and, better yet, experimental studies before we can generalize the result.

Graboys et al assert the Holter- and exercise-guided antiarrhythmic treatment is more practicable, cost-effective, and widely applicable than electrophysiologic guided treatment. Certainly, some highly organized program is warranted for patients with life-threatening ventricular arrhythmias, and the 2 most appealing candidates are Holter-guided and electrophysiologic-guided treatment. However, we believe their assertion is debatable. Therefore, we will compare these 2 methods briefly in terms of patient selection, endpoints, ease of antiarrhythmic drug selection, safety assessment, compliance evaluation, complexity, and cost.

Patient selection: Both methods are inconvenient and costly so that only patients who have significant symptoms or risk of mortality or morbidity risk should be selected. A Holter- or telemetry-guided approach is clearly better for patients with incessant ventricular tachycardia. The electrophysiologic method is preferable for patients who have infrequent episodes of ventricular tachycardia or ventricular fibrillation or those with a very low frequency of ventricular premature depolarizations (VPD). For many patients either method can be used.

Endpoints: The Holter-exercise method as advocated by Graboys et al uses total abolition of Lown grade 4B or 5 arrhythmias as the criterion for successful drug treatment. This is not a simple objective. Graboys et al have painstakingly developed a method for detecting repetitive and R-on-T VPD in 24-hour electrocardiographic (ECG) recordings. However, routine clinical analysis of 24-hour ECG recordings misses many of the episodes of ventricular tachycardia,[2] and even research arrhythmia detection systems have difficulty in reliably detecting the R-on-T phenomenon. There is little risk in Lown grade 5 for those patients who do not have repetitive VPD.[3] These problems do not adversely affect the results reported by Graboys et al, but they do limit very significantly the widespread application of the method. In electrophysiologically guided treatment, success is defined as abolition of inducible ventricular tachycardia or fibrillation. Nonsustained ventricular tachycardia less than 6 complexes in duration also is considered a success. With either method the endpoint is relatively crisp, but the endpoint is more difficult to determine by Holter techniques.

Ease of drug selection: Graboys et al test for efficacy in 2 phases: (1) acute drug testing, and (2) short duration maintenance. Acute drug testing requires 6 to 7 hours of observation and trendscription along with many determinations of serum drug concentration. An average of 6 acute drug tests are required per patient. Phase 2 testing requires 48 to 96 hours for each drug tested (many drugs can only be tested in phase 2) and multiple Holter ECG recordings and exercise tests. Finally, 2 or more drugs that were effective singly are given together for long-term treatment. Multiple drug use is based on the failsafe concept. However, adverse drug interactions also can result from this practice. Electrophysiologic testing requires a day between drug trials to permit the body to eliminate antiarrhythmic drugs. Each test session takes 2 to 4 hours because dose ranging with repeated stimulation is usually performed. Usually, 2 effective drugs are sought but only 1 is used for long-term treatment. The process of drug selection is somewhat simpler to interpret with the electrophysiologic method. Both methods have significant, but poorly defined, reliability problems, that is, between-day variance. In theory, drugs may prevent ventricular tachycardia by reducing the VPD which trigger tachyarrhythmias or by increasing the tachycardia or fibrillation threshold so that VPD can no longer initiate malignant arrhythmias, or by both actions. The Holter approach may show a marked reduction in VPD frequency when electrophysiologic studies show the ventricle to be still inducible. Conversely, inducibility by programmed ventricular stimulation may be abolished even though VPD do not reach the criteria for successful treatment used by Graboys et al.

Safety assessment: Holter-guided therapy may identify patients whose ventricular arrhythmias are worsened by antiarrhythmic drug treatment.[4] However, recognition is hampered by between-day variability in arrhythmia rates. Holter recordings also are excellent for detecting adverse drug effects on the sinus node, atrioventricular node, and His-Purkinje system. Electrophysiologic studies are excellent for detecting aggravation of the target arrhythmia. Also, the electrophysiologic method can detect the patient whose ventricular premature depolarizations and nonsustained ventricular tachycardia improve markedly while his sustained ventricular tachycardia becomes easier to induce or more life-threatening; this situation cannot be detected by the Holter method. The electrophysiologic method is probably more sensitive in detecting adverse drug effects on cardiac automaticity and conduction. Given the high rate of adverse effects with currently available antiarrhythmic drugs, both methods should be used in many patients with life-threatening ventricular arrhythmias.

Compliance evaluation: As a rule, patients with life-threatening arrhythmias are very compliant with treatment recommendations. Holter recordings can be used to assess patient compliance and arrhythmia stability during follow-up. Electrophysiologic studies are more cumbersome to use in this way. Usually, electrophysiologic studies are not repeated during follow-up unless symptoms or arrhythmias recur. For both methods, serum drug concentrations are conve-

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

nient and useful adjuncts for evaluating compliance.[5]

Complexity: Both Holter-exercise and electrophysiologic approaches are reasonably complex; their degree of complexity is quite similar. Both methods require well-organized, often-used programs for efficiency and effectiveness. It is unreasonable to assume that physicians who only occasionally see patients with malignant arrhythmias can effectively use either method without assistance.

Cost: There is no significant difference in cost between the Holter-exercise program recommended by Graboys et al and electrophysiologic approaches. The cost of the large number of 24-hour ECG recordings and exercise tests used by Graboys et al[1] often would exceed the cost of serial electrophysiologic testing plus a few adjunctive Holter ECG recordings. Both techniques make liberal use of serum drug concentration measurements. The hospital stay is approximately equal for the 2 methods, with the average stay being somewhat shorter for the electrophysiologic method. The hospital stay can be longer with the electrophysiologic method when all drugs fail. The longer stay can be attributed to the additional time required for arrhythmia surgery or implantation of an automatic defibrillator. However, these avenues of treatment also are appropriate for drug failures in the Holter-exercise approach.

Summary: Empirical management of patients with malignant ventricular arrhythmias is unsatisfactory. Therapy must achieve endpoints that predict improved likelihood of survival. Both the Holter-exercise approach and the electrophysiologic approach have been proposed for this purpose, but there have been no controlled comparisons of these 2 methods. Graboys et al cite some of the several studies that demonstrate the effectiveness of the electrophysiologic approach. Now that the Holter-exercise method has been reported effective by Graboys et al, we must compare this alternative with the better-established electrophysiologic method with respect to efficacy, efficiency, and safety. There appears to be no significant difference in the cost of the 2 approaches. Both methods are complex enough to warrant the recommendation that they be employed by experienced groups. We must await future comparative studies, hopefully experimental ones, to define any overall preference between these 2 approaches or to combine elements of each into a single program.

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REPLY: We welcome Bigger and Reiffel's carefully honed argument questioning some of the conclusions of our study. Their thoughtful analysis demands a detailed response, especially since the issues raised are of pressing contemporary relevance. But before joining the dialogue, it needs to be stressed that the points they dispute are quite peripheral to the central motif of our presentation.

Our study reported 2 essential findings: (1) that patients having sustained malignant ventricular arrhythmias can be protected against recurrence by tailoring antiarrhythmic drug therapy to the individual patient, and (2) that the selection and dosing with an appropriate drug can be guided by reduction in prevalence of ventricular premature beats and more specifically by elimination of their advanced grades. To achieve this therapeutic objective we devised a number of new methods. Bigger and Reiffel only tangentally deal with the essential objectives and the underlying hypothesis.

Bigger and Reiffel preface their main objections with a number of diverse criticisms, and these need to be disposed of first. They complain that ours was an observational, not an experimental study. They thereby posit spurious levels of revealed truth. A sound observation is certainly to be preferred to a shoddy experiment. Even beyond the casuistry, how is one to conduct an experimental study in patients who have identified themselves as being at imminent risk for sudden cardiac death? Does not protection of survival take precedence over nearly all other considerations?

Bigger and Reiffel fault our study for dealing with highly selected patients. Indeed, this is the case of any hospital-based study with its complex referral pattern. This truism in no way vitiates the findings if the sample population is adequately defined. They complain of the incompleteness of hemodynamic data. We agree. Nevertheless, among 44 patients who had substantiated hemodynamic impairment demonstrating markedly reduced ejection fractions, control of ectopic activity continued as a critical determinant of survival.

Bigger and Reiffel furthermore demand randomization and systematic assignment to alternative treatment regimens, details about drug sequencing and selection, the use of drug combinations, the employment of digitalis, data on long-range adverse drug effects, changes to new treatment schedules, and so on. In effect, they throw the book at us for not having written a different and more encyclopedic article. Some of these questions are answered in other recent reports.[1–5]

But the very questions they do pose indicate a failure to grasp our essential thesis: that it is not a particular antiarrhythmic agent which is decisive; rather, any drug which reduces ventricular premature beats of advanced grade will improve survival. We are delighted that "these flaws are tolerable" and can turn now to the central issue.

Bigger and Reiffel question primary reliance on Holter-exercise studies for drug selection to treat malignant ventricular arrhythmias. They prefer electrophysiologic testing. One searches in vain in their long letter for evidence to buttress this viewpoint. Their final words indicate a different conclusion. They suggest the need for comparative studies of the 2 approaches to define "overall preferences." As no such data exist, why prefer one method to another until the evidence has been marshalled? Hence, the collateral points raised by Bigger and Reiffel are of some consequence and deserve systematic examination.

Patient selection: Bigger and Reiffel acknowledge that patients with frequent paroxysms of ventricular tachycardia do not require electrophysiologic studies, presumably because monitoring is less costly and traumatic than an invasive approach. Would it not be sensible to extend the same logic to those with frequent and reproducible ventricular premature beats? We would readily agree that at the other extreme of the spectrum, those who have had potentially lethal ventricular arrhythmias but are free of reproducible ventricular ectopic activity require electrophysiologic studies. Among 260 patients with recurrent malignant ventricular arrhythmias, we have had to resort to electrophysiologic testing in 52 (20%) because of a paucity of ectopic activity.

Endpoints: The impression conveyed is that the electrophysiologic method is standardized, reproducible, and has a well-defined endpoint. As far as we know no consensus exists as to the number of pulses, the current level, the pacing rate, the precise locus for stimulation, the need for multiple sites, or what constitutes sustained ventricular tachycardia. We would welcome reference to rigorous studies defining specificity and sensitivity of electrophysiologic testing with a standardized method and a predetermined endpoint. At the 55th Scientific Session of the American Heart Association, the presentation dealing with electrophysiologic testing sounded more like that at a Tower of Babel than like scientific reports of a method with a "crisp" endpoint.

A basic problem with electrophysiologic testing that precludes a precise endpoint is that the elicited response represents part of a biologic continuum relating largely to properties of the test stimulus. It is difficult to define rigorously a normal or abnormal response when ventricular tachycardia and fibrillation can be provoked in the normal heart as a function of current strength, the pacing rate, and the sequencing of stimuli. The spectrum of response among those with arrhythmia and diverse forms of heart disease is unknown. Therefore to adduce exactitude to this approach at best is premature and most probably will prove elusive.

Ease of drug selection: In choosing a drug one must be attuned to its pharmacokinetic and pharmacodynamic properties. While drug efficacy may be judged by an electrode catheter, this affords information only for the particular avenue of administration for 1 point in time, and for a single employed dose level. Furthermore, it does not predict patient tolerance during chronic drug administration. Our Phase 1 and Phase 2 provide the clinician

with more comprehensive information on drug response and tolerance over 24 hours and permit greater flexibility than is to be gained during a brief electrophysiologic study. In addition, with some drugs studied electrophysiologically there is disparity between tests results and clinical outcome. This is true with amiodarone and perhaps also with encainide. We have not encountered such a phenomenon with our method.

Safety assessment: Bigger and Reiffel disregard an important element in our methodology: acute drug testing (Phase 1). This phase facilitates recognition of adverse drug effects without the need for Holter monitoring and can be readily performed at the bedside.[6] The follow-through with Phase 2 study enhances this type of information, precluding frequent and costly rehospitalizations for adverse drug reactions. Ascribing special virtue to electrophysiologic testing for recognizing arrhythmia aggravation is astonishing when one considers the paucity of meaningful data.

Compliance evaluation: Bigger and Reiffel admit the superiority of the Holter-exercise method in follow-up, but this admission underscores the illogic of their position. In the real world, outside academia, life does not proceed on a predictable and smooth trajectory. There arise needs for other medications, the patient confronts bereavement and diverse physical and emotional stresses, infection and other illness may occur, and a host of other events can modify the mode of action of the administered antiarrhythmic. How is the physician to judge whether protection is still being afforded? Suppose the antiarrhythmic agent provokes symptoms and the dose needs adjustment: how is one to assess continued drug efficacy? In dealing with a potentially lethal arrhythmia, is it permissible to indulge the luxury of an educated guess? Does not the electrophysiologic approach encourage frequent and costly rehospitalization to assure the physician, under the aforementioned circumstances, that drug effectiveness is maintained?

But here the cross-stitch of logic is completely tattered. Bigger and Reiffel counsel Holter monitoring. Is life less valued for the outpatient to justify resorting to an inferior method of evaluation? They do not delineate the endpoint to be sought with Holter monitoring. Is one to be attentive to mere presence of ectopic beats, to their frequency, to the occurrence of advanced grades, or to only paroxysms of tachycardia? And once the selected endpoint is to be exposed, what may be inferred as to the efficacy of the antiarrhythmic drug being employed? Without prior experience with Holter or exercise testing during initial drug use, how is one to draw sensible therapeutic inferences? If treatment modification is to be affected by Holter-exercise findings during follow-up, one would surmise that it is equally appropriate to employ these methods during initial drug selection. Or are we to conclude that in the real world Bigger and Reiffel would resort to repeated costly hospitalizations for executing electrophysiologic studies?

Complexity: The argument relating to complexity batters at an open door. We have not suggested that treating patients with life-threatening arrhythmias is a simple endeavor. It requires a careful program as well as much expertise. We believe the issue is of a different sort. Patients afflicted with recurring malignant ventricular arrhythmias constitute a miniscule subset of those threatened with sudden death. While the electrophysiologist is concerned with the former, the practicing cardiologist and internist confront the latter. At present the most practicable method for identifying the coronary heart disease patient at risk for sudden death is by exposing the presence of advanced grades of ventricular premature beats by means of Holter-exercise methods. The system of treatment which we have evolved is primarily intended for application by physicians encountering patients at risk for sudden death. Behind the facade of words there may be a subtle struggle over turf.

Cost: This last point raised by Bigger and Reiffel is especially astonishing since the cost of an electrophysiologic study is far greater than that of Holter and exercise tests combined. Ross et al[7] in 1980 estimated electrophysiologic testing to cost $800. But the approach of Bigger and Reiffel requires the employment of both methods: "Given the high rate of adverse reactions with currently available antiarrhythmic drugs, both methods should be used in many patients with life-threatening ventricular arrhythmias." They may find an escape hatch with the word "many," but if the dual approach is optimal for some such cases, why should it not be employed in all? Certainly it is sheer casuistry to imply that the use of 2 methods may be less expensive than either.

An aspect completely ignored by Bigger and Reiffel relates to the human cost. Where in all this discussion is the patient—the invaded, frightened, psychologically stressed patient? In the series of Mason and Winkle,[8] 52% of patients studied electrophysiologically required emergency cardioversion because of accelerating rate or hemodynamic instability. Speilman et al[9] encountered ventricular fibrillation in 10 (15%) of 68 patients who were being subjected to extrastimuli testing for recurrent ventricular tachyarrhythmias. Horowitz et al[10] reported the need for emergency cardioversion in 21%. These are profoundly traumatic experiences not easily forgotten, which in some patients become the psychologic trigger for the very arrhythmia we aim to prevent. There are, of course, other complications such as deep venous thrombosis and pulmonary emboli (4.4%), local or systemic infections (2.9%), and pneumothorax (2.4%).[11] While there are no cardiac enzyme changes induced by electrophysiologic testing, terror in the human heart is not readily assessed by such biochemical means.

In summary: The ventricular premature beat provides a suitable target for antiarrhythmic drug selection, dosing, and adjustment in hospital and in later follow-up. The method is especially powerful when both Holter monitoring and exercise testing are employed to assess drug response. Abolition of advanced grades of ventricular premature beats affords protection in those at high risk for sudden death. Our initial report dealing with 123 patients has now been extended to more than 300 patients, and the results continue as reported. In a small subset of 20%, electrophysiologic testing is mandated by the paucity of ectopic activity. We concur with Bigger and Reiffel's last sentence suggesting the need for comparative studies. It is our conviction, though, that the specific presentation of a clinical problem must guide in the choice of a particular methodology.

Bernard Lown, MD
Thomas B. Graboys, MD
Philip J. Podrid, MD
Boston, Massachusetts

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HYPERPROLACTINEMIA-GALACTORRHEA INDUCED BY VERAPAMIL

In 1981 a single case of verapamil-induced hyperprolactinemia and galactorrhea was reported.[1] As part of our participation in the clinical evaluation of verapamil by Knoll Pharmaceutical, we studied the drug in 7 women and 1 man. Clinical galactorrhea developed in 3 of the 7 women and hyperprolactinemia or galactorrhea, or both, developed in 6. The serum level in the 1 man was normal. The appearance of galactorrhea did not correlate with the degree of elevation of serum prolactin. No woman had amenorrhea or abnormal thyroid studies or was taking medications known to induce hyperprolactinemia or galactorrhea such as methyldopa, oral contraceptives, reserpine, or phenothiazines. One patient with galactorrhea was taken off verapamil, and the galactorrhea completely disappeared. She was subsequently placed on nifedipine with no resumption of galactorrhea. In the absence of hypothyroidism or elevated thyrotropin-releasing hormone (TRH), the most logical mechanism for verapamil hyperprolactinemia would be interference with the release or synthesis of prolactin inhibitory factor in the hypothalamus.[2,3]

Galactorrhea, usually with amenorrhea, may occur spontaneously (Argonz-del-Castillo syndrome) in the postpartum state (Chiari-Fromel syndrome) or may be asso-

ciated with pituitary tumors (Forbes Albright syndrome).[2,4]

This study confirms the development of hyperprolactinemia in 6 and galactorrhea in 3 women initially treated with verapamil. In none did amenorrhea develop, which may be a diagnostic point in support of verapamil hyperprolactinemia-galactorrhea as opposed to other causes of this syndrome.

This study confirms that hyperprolactinemia and galactorrhea are frequently associated with verapamil therapy. Because of the excellent response to verapamil, it was medically inadvisable to withdraw therapy to evaluate prolactin levels off medication. The true frequency of hyperprolactinemia and galactorrhea associated with verapamil therapy is unknown, but on the basis of our study it occurs in a significant number of patients. With the increasing number of women being placed on verapamil therapy for recurrent paroxysmal supraventricular tachycardia, the association of hyperprolactinemia and galactorrhea with this therapy should be recognized.

Eric L. Fearrington, MD
Cecil H. Rand, Jr., MD
John D. Rose, MD
Greenville, North Carolina

1. **Gluskin LE, Strasbert B, Shah J.** Verapamil induced hyperprolactinemia and galactorrhea. Ann Intern Med 1981;95:66–67.
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SUDDEN DEATH IN A MARATHON RUNNER WITH ORIGIN OF THE RIGHT CORONARY ARTERY FROM THE LEFT SINUS OF VALSALVA

We read with interest the article by Roberts et al[1] in your March 1982 issue which dealt with the origin of the right coronary artery from the left sinus of Valsalva and its functional consequences. We recently were involved in a case of sudden death in a 26-year-old marathon runner who was training for the Iron Man Triathalon in Hawaii. He had been swimming, exercising, weight lifting, and marathon running and collapsed just past the finish line of a 13.5 mile marathon. The anatomic findings were identical to those described by Roberts et al and included a slit-like right coronary ostium and a flattened right coronary artery which coursed between the aorta and pulmonary artery. The anomalous right coronary artery supplied both the atrioventricular and sinoatrial nodes and was the dominant coronary artery. All 4 cardiac chambers were hypertrophic and the heart weighed 420 g. The decedent had had at least 2 episodes of shortness of breath after long runs, which was atypical of his normal postmarathon experience, but he attributed the symptoms to inadequate fluid intake.

The details of this case were reported in the March 1983 issue of *The American Journal of Forensic Medicine and Pathology*. The case further supports the opinion of Roberts et al that anomalous origin of the right coronary artery from the left sinus of Valsalva can no longer be considered a minor congenital anomaly of no clinical significance, as it may be associated with sudden death in young and otherwise healthy persons.

Randy Hanzlick, MD
Robert R. Stivers, MD
Atlanta, Georgia

1. **Roberts WC, Siegel RJ, Zipes DP.** Origin of the right coronary artery from the left sinus of Valsalva and its functional consequences: analysis of 10 necropsy patients. Am J Cardiol 1982;49:863–868.

PROLONGATION OF Q-T INTERVAL AND INCREASED AMPLITUDE OF THE T WAVE AFTER TERMINATION OF VENTRICULAR TACHYCARDIA

Soffer et al[1] described (in their Figure 2) a patient with ventricular tachycardia (VT) and noted prolongation of the Q-T interval following the first beat after cessation of VT. The T wave of this beat was taller than that of the subsequent sinus beats. The following description pertains to a 1-day-old male infant in whom short runs of VT developed at birth. He was asymptomatic, without precordial murmurs, and had a normal-sized heart and normal pulmonary vascularity. Serum electrolytes, including calcium and magnesium, were normal. The surface electrocardiogram showed an axis of +120° with no evidence of atrial or ventricular hypertrophy. The Q-T interval was 0.40 second (Q-Tc = 0.54 second) during sinus rhythm, and the T wave was flat in all 12 leads. The Q-T interval of the first beat after termination of VT (Fig. 1) was still 0.40 second (Q-Tc = 0.56 second), but the T wave was taller than that of the subsequent sinus beats. The T wave of the last beat of the VT also was tall. These findings were consistently observed after termination of every short run of VT. The patient has been treated with propranolol for 1 year and the Q-T interval has normalized. Thus, a prolonged Q-T interval is associated with VT.

The finding of a tall T wave in the first beat after termination of VT as well as in the last beat of VT is unusual. Cohen et al,[2] by microelectrode technique, studied the action potential duration of the upper part of the ventricular septum and the epicardial surface of the apex of the left ventricle of sheep to clarify the genesis of the polarity of the T wave of the surface electrocardiogram. They found that the steady-state action potential duration of the apex of the left ventricle was shorter than that of the upper part of the septum. This difference would account for a positive T in the electrocardiogram. This phenomenon of a longer Q-T interval in the first beat after cessation of VT associated with increased amplitude of the T wave may

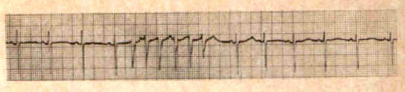

FIGURE 1. Electrocardiographic lead II reveals a tall T wave in the last beat of VT and in the first sinus beat after termination of the arrhythmia in my patient.

be secondary to differences in the action potential duration of different ventricular sites. These differences were probably markedly increased because in both patients VT ceased just before the described findings. These findings imply that the mechanism of VT in both patients was reentry. In the patient reported on by Soffer et al,[1] the Q-T interval and the amplitude of the T wave decreased once sinus rhythm was established. In my patient, the T wave flattened after resumption of sinus rhythm. These findings might be explained by more uniform depolarization of the ventricles during sinus rhythm.

Prolongation of the Q-T interval in the first sinus beat after cessation of VT and the tall T wave observed in the last beat of VT and the first sinus beat after termination of VT may give clues about the mechanism of the dysrhythmia.

Alfonso Casta, MD
Galveston, Texas

1. **Soffer J, Dreifus LS, Michelson EL.** Polymorphous ventricular tachycardia associated with normal and long Q-T intervals. Am J Cardiol 1982;49:2021–2029.
2. **Cohen I, Giles W, Noble D.** Cellular basis for the T wave of the electrocardiogram. Nature 1976;262:657–661.

REPLY: We are pleased that Casta recognized a phenomenon similar to that described in our report. Unfortunately, there is no accepted reason for this electrophysiologic observation. I doubt that the observations of Cohen et al are related to these findings in the clinical electrocardiogram.

Leonard S. Dreifus, MD
Joseph Soffer, MD
Eric L. Michelson
Philadelphia, Pennsylvania

PTCA: NEED FOR PROSPECTIVE RANDOMIZED CONTROLLED TRIALS

The report from the National Heart, Lung, and Blood Institute (NHLBI) registry of percutaneous transluminal coronary angioplasty (PTCA) is an impressive document, if only for its 17 authors.[1] As an invited commentator at the NHLBI Conference in June 1981 from which this work emanates, I was duly impressed by the attractive—even seductive—results. Yet, it is distressing that the distinguished authors do not at least mention the possibility of, let alone the necessity for, appropriately designed prospective randomized controlled trials of PTCA. I raised that issue at the Conference and it was fairly intensely discussed—though, to be sure, probably not agreed to by most of those actually doing the procedure (no votes were taken). The issue is even more sharply drawn when we read the words of Dr. Gruentzig, an author of this report and the brilliant pioneer of the method: "However, the results in pa-

tients with single-vessel disease are sufficiently good to make the procedure acceptable for prospective *randomized trials. Such trials are clearly needed* if we are to evaluate the efficacy of this new technique as compared with current medical and surgical treatments"[2] (emphasis mine). When this unambiguous statement was cited on a slide at the Conference, the reply (not only from Dr. Gruentzig) was that patients were being referred specifically for the procedure and it could not be denied to them. (One wonders whether such unambiguous statements—and there are many[3]—appended to papers in prestigious journals are more of a victory for "revision accepted" than "principle accepted").

The foregoing in no way denigrates the careful and otherwise scientifically sound work that has been done by Gruentzig, Myler, and the many other excellent cardiologists who have proceeded with PTCA step by step and deliberately, rather than with the unseemly haste that characterizes too many innovators. Yet it is these outstanding workers, with the highest prestige in the field, who are best qualified to perform appropriately designed trials, so that we will have acceptable denominators for the numerators that they have generated with such care—not to mention the expected avalanche of numerators, now that the genie is well out of the bottle. I suspect that if most of us had a lesion amenable to PTCA we would prefer PTCA to bypass if we could be sure PTCA was better in the long run. (The authors have established its relative safety[1]). Until that is accomplished, PTCA remains a brilliant technical *tour de force* of great promise.

All therapeutic innovations are of uncertain value when we expose the first patient to them; we have hopes, but cannot then know the short-term, and especially the long-term, results. This mandates controlled clinical trials, scientifically and ethically, from the very first patient. "Learning curves" and adjustments in dosage and technique do not invalidate that concept, since with random allocation to innovation or standard treatment, it requires only *patience* on the part of the investigator. It would merely take twice as long as in an uncontrolled trial (including changes in method), since half the patients would be in the control group—the genuine denominators that should make the results unimpeachable. Thus, from Patient Number One on, all patients would get a 50-50 chance to receive best treatment, which ultimately becomes the new treatment or established treatment. This approach—mandatory with pills and injections—requires a little patience but, if successful, it should eliminate the necessity for letters like this one.

David H. Spodick, MD, DSc
Worcester, Massachusetts

1. **Kent KM, Bentivoglio LG, Block PC, et al.** Percutaneous transluminal coronary angioplasty: report from the registry of the NHLBI. Am J Cardiol 1982;49:2011–2020.
2. **Gruntzig AR, Senning A, Siegenthaler WE.** Nonoperative dilatation of coronary artery stenosis. N Engl J Med 1979;301:61–68.
3. **Spodick DH.** The randomized controlled clinical trial: scientific and ethical bases. Am J Med 1982;73:420–425.

REPLY: Spodick has again[1] correctly emphasized the value of randomized studies to elucidate therapeutic procedures. In answer to his former letter,[2] we tried to encourage others to help us to formulate a protocol for randomization because the call for randomization is easily made but difficult to follow, especially in centers in which patients are referred from other centers for this special procedure and not for randomization. And, as we pointed out, each referring center should therefore randomize its own cases before referral is made. In addition, one must create 3 groups of matched patients: medical, surgical, and angioplasty, if Spodick had such a study in mind. As we all know, crossovers in these 3 subsets are a burden and occur because these forms of therapy are intrinsically different. For instance, after coronary dilatation as well as after coronary bypass surgery, almost 50% of our patients remain on medical therapy, so it is difficult to cleanly separate the effects of revascularization and medical therapy.

The problem is therefore what to randomize the patients to besides PTCA. The vast majority of our patients have unsatisfactory control of symptoms despite medical therapy or very proximal LAD stenosis with a large mass of myocardium at risk. Even though our surgery is excellent at Emory University, it is still associated with a 0.4% mortality and a 4.4% incidence of Q-wave infarction in single-vessel disease.[3] For our entire series of over 1,100 cases (90% single-vessel disease), we have had 1 in-hospital death (0.1%) which was noncardiac and a 2.1% incidence of Q-wave infarction. For the last 300 cases we have had 2 Q-wave infarctions (0.7%). These results underline the report of the National Institutes of Health PTCA Registry[4] and establish the relative safety of the procedure. Faced with these results, we do not see the need for a randomization of this subset of patients, but it might be needed for other subsets, such as those with multivessel disease. In regard to the long-term benefits, prospective studies are underway to determine the patency of vessels after angioplasty. These results will be compared with the patency of bypass grafts already well known from published reports.

We do believe in the randomized trial for difficult and important medical questions. We are using this valuable instrument to explore the effects of various therapies on our primary and long-term results. In our hospital, randomized studies are currently underway to test the effect of exercise training and various drug regimens in the prevention of recurrent stenosis. We are testing by randomized studies the effect of streptokinase infusion for myocardial salvage in acute myocardial infarction.

Andreas R. Gruentzig, MD
Jay Hollman, MD
Atlanta, Georgia

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4. **Kent KM, Bentivoglio LG, Block PC, et al.** Percutaneous transluminal coronary angioplasty: report from the registry of the NHLBI. Am J Cardiol 1982;49:2011–2020.

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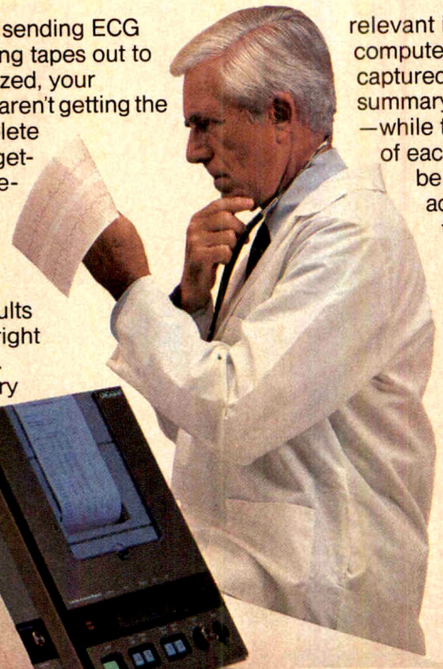

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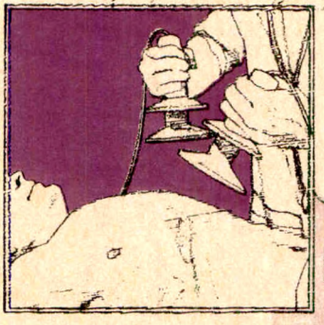

For further information, please contact the Medical Services Department, American Critical Care, a division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

*based on laboratory animal studies

1. Bacaner, M.B., *Am. J. Cardiol.*, *21*(4):504-512, April, 1968. 2. Cardinal, R. and Sasyniuk, B.I., *J. Pharmacol. Exp. Ther.*, *204*(1):159-174, 1978. 3. Tacker, W.A., Niebauer, M.J., Babbs, C.F., Combs, W.J., Hahn, B.M., Barker, M.A., Seipel, J.F., Bourland, J.D. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979. 4. Babbs, C.F., Yim, G.K.W., Whistler, S.J., Tacker, W.A. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979.

Bretylol...adds a different and unique dimension in control of ventricular fibrillation

American Critical Care

Bretylol®
(bretylium tosylate)

Brief summary of prescribing information

INDICATIONS—BRETYLOL is indicated in the prophylaxis and therapy of ventricular fibrillation.

BRETYLOL is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS—**1. Hypotension:** Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY—The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN—The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS—**1. Dilution for Intravenous Use:** BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use of Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

ADVERSE REACTIONS—Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

Oct. 1980

Please refer to complete prescribing information prior to use.

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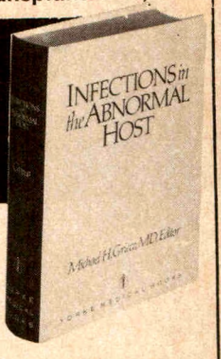

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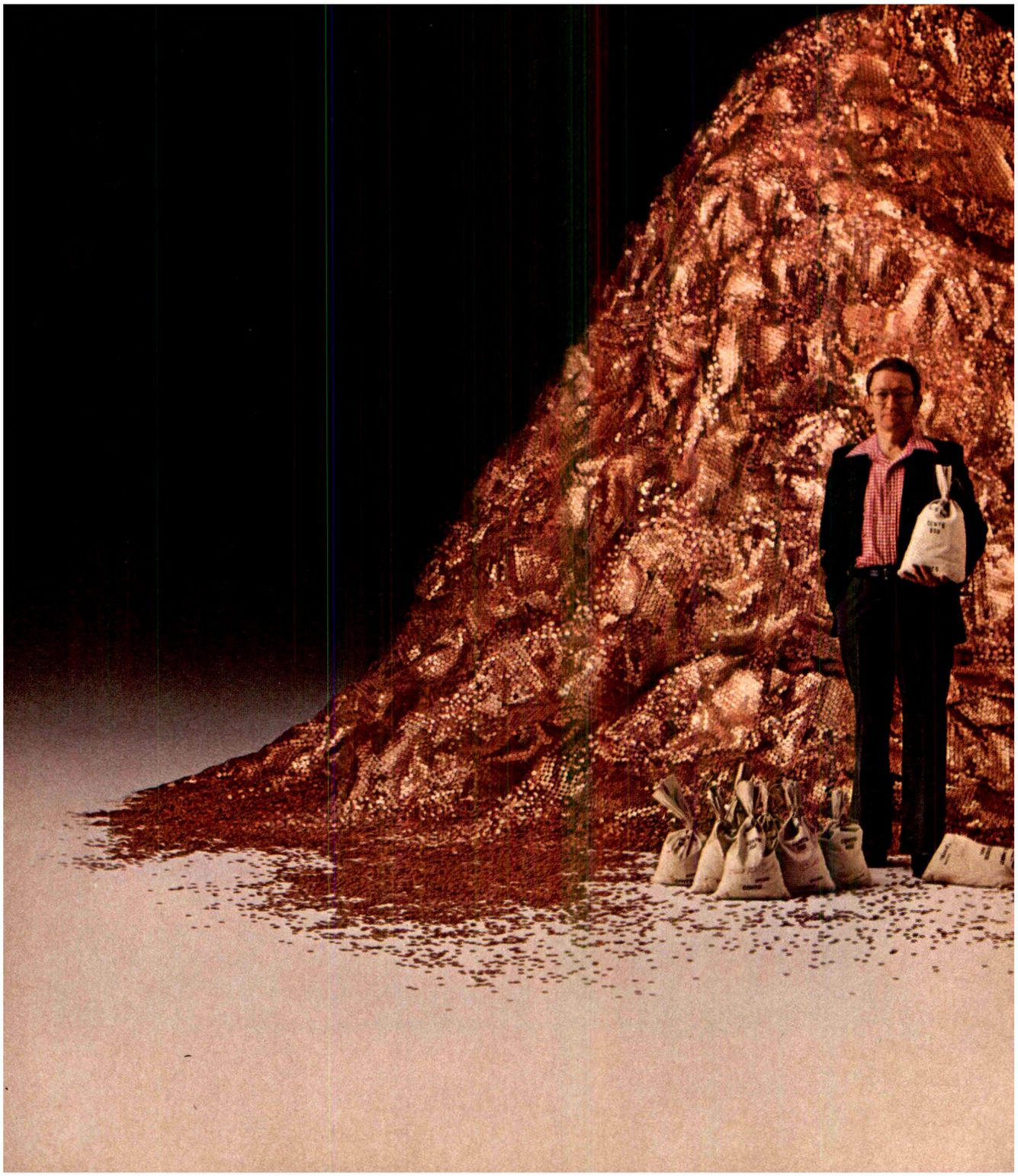

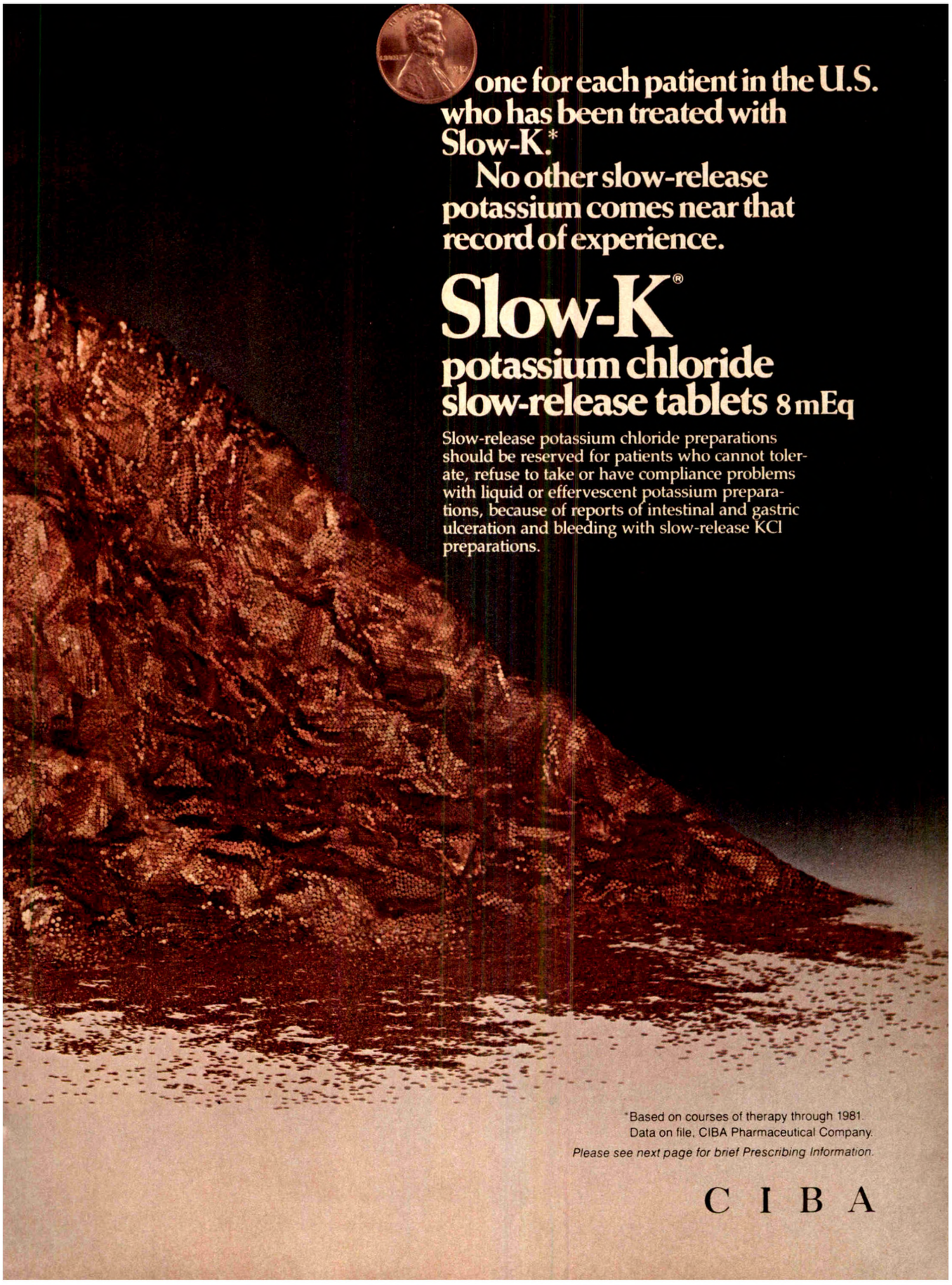
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*Based on courses of therapy through 1981. Data on file, CIBA Pharmaceutical Company.
Please see next page for brief Prescribing Information.
CIBA

SLOW-K®
potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

Consult complete product literature before prescribing.

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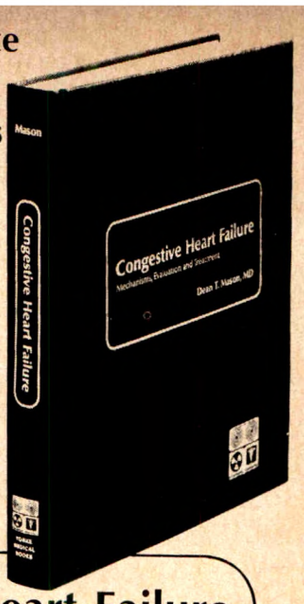

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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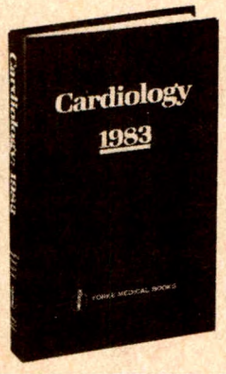

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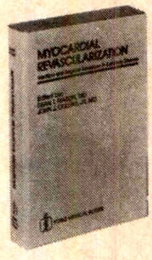

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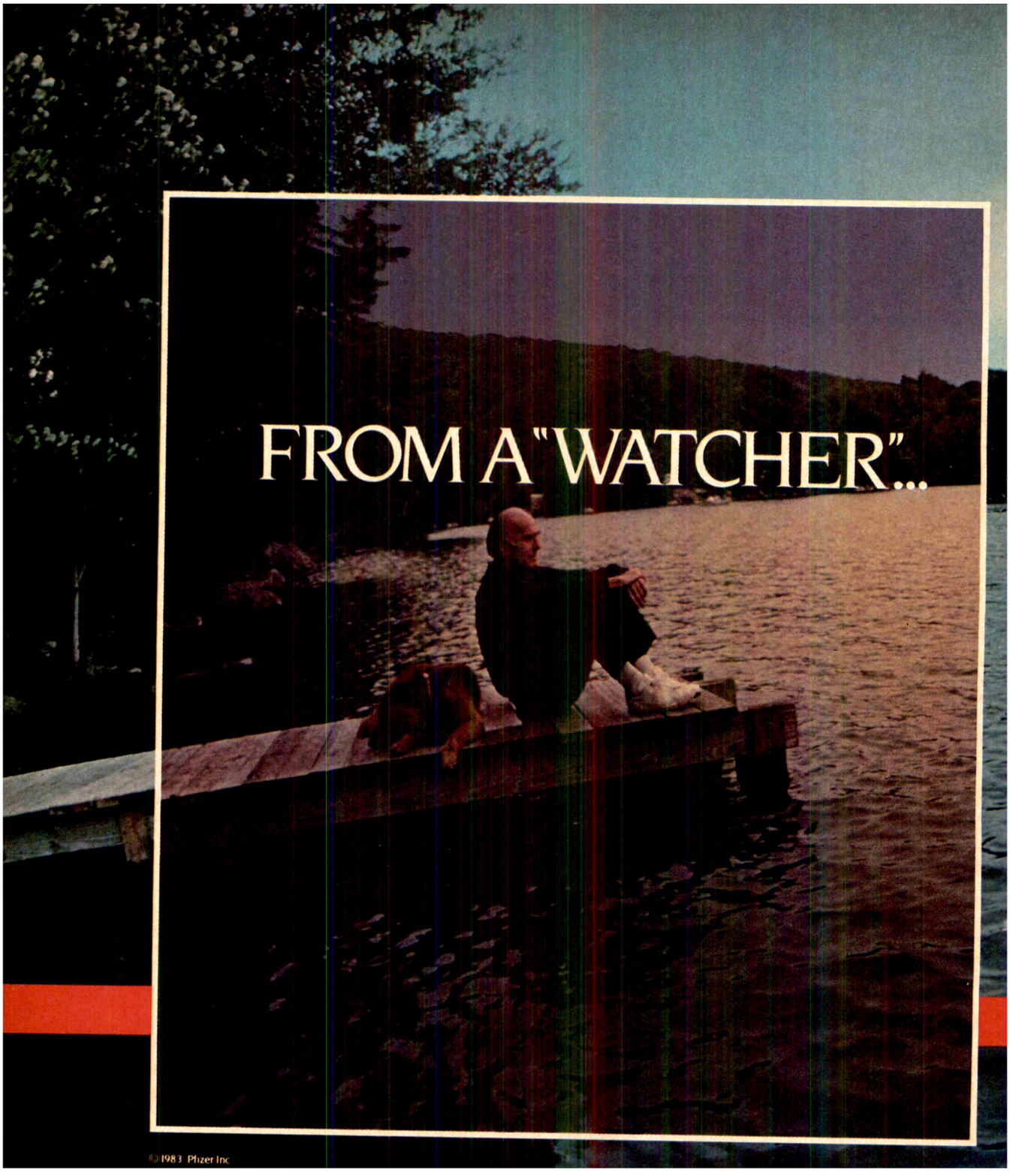

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PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:

- Confirmed vasospastic angina.
- Angina where the clinical presentation suggests a possible vasospastic component.
- Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) Procardia has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

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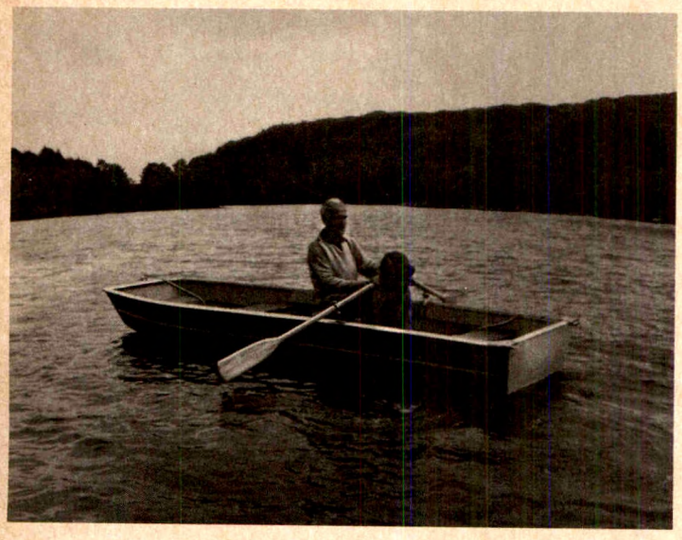

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

–Usual effective dosage is 30-60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.

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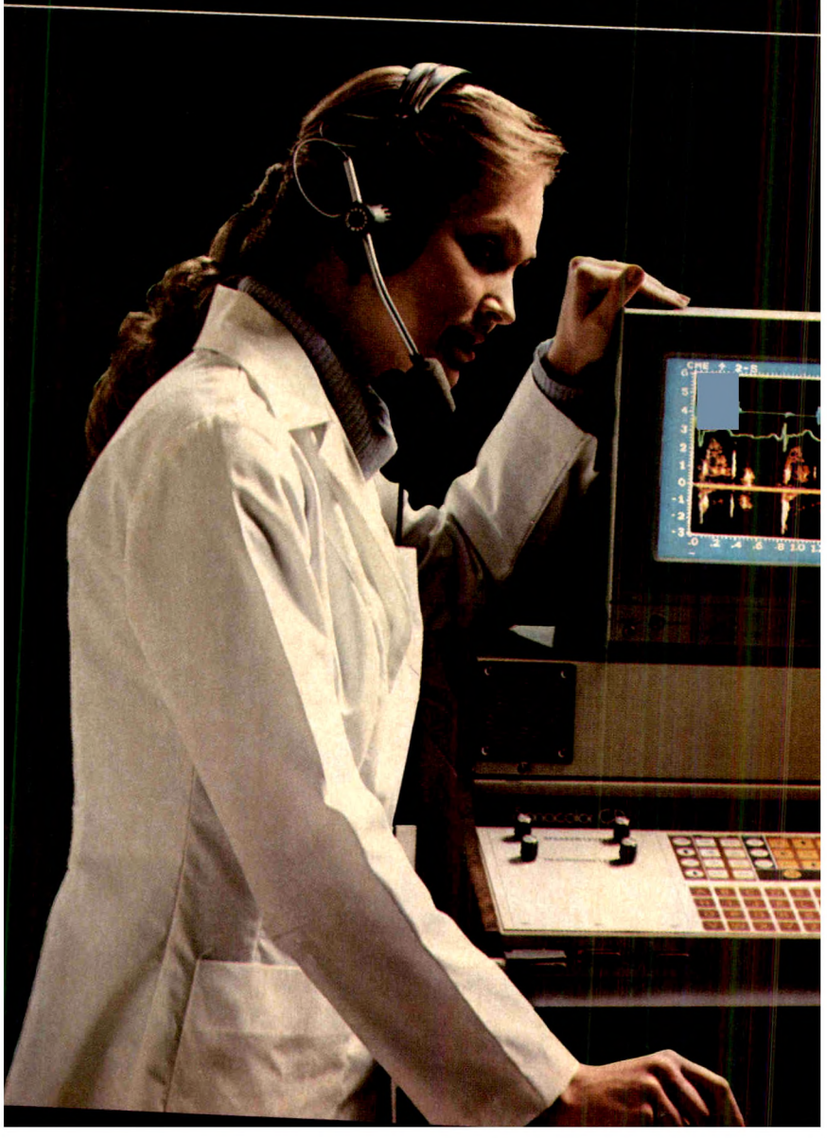

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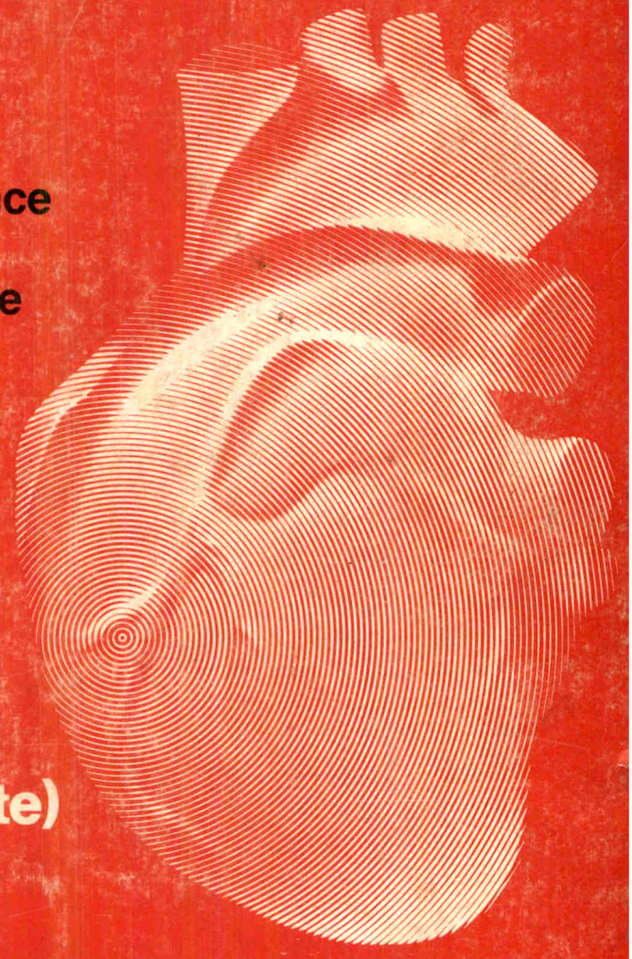

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations.
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digoxin (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: The drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/or disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTESTINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricular tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMATOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intense pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribing Information.

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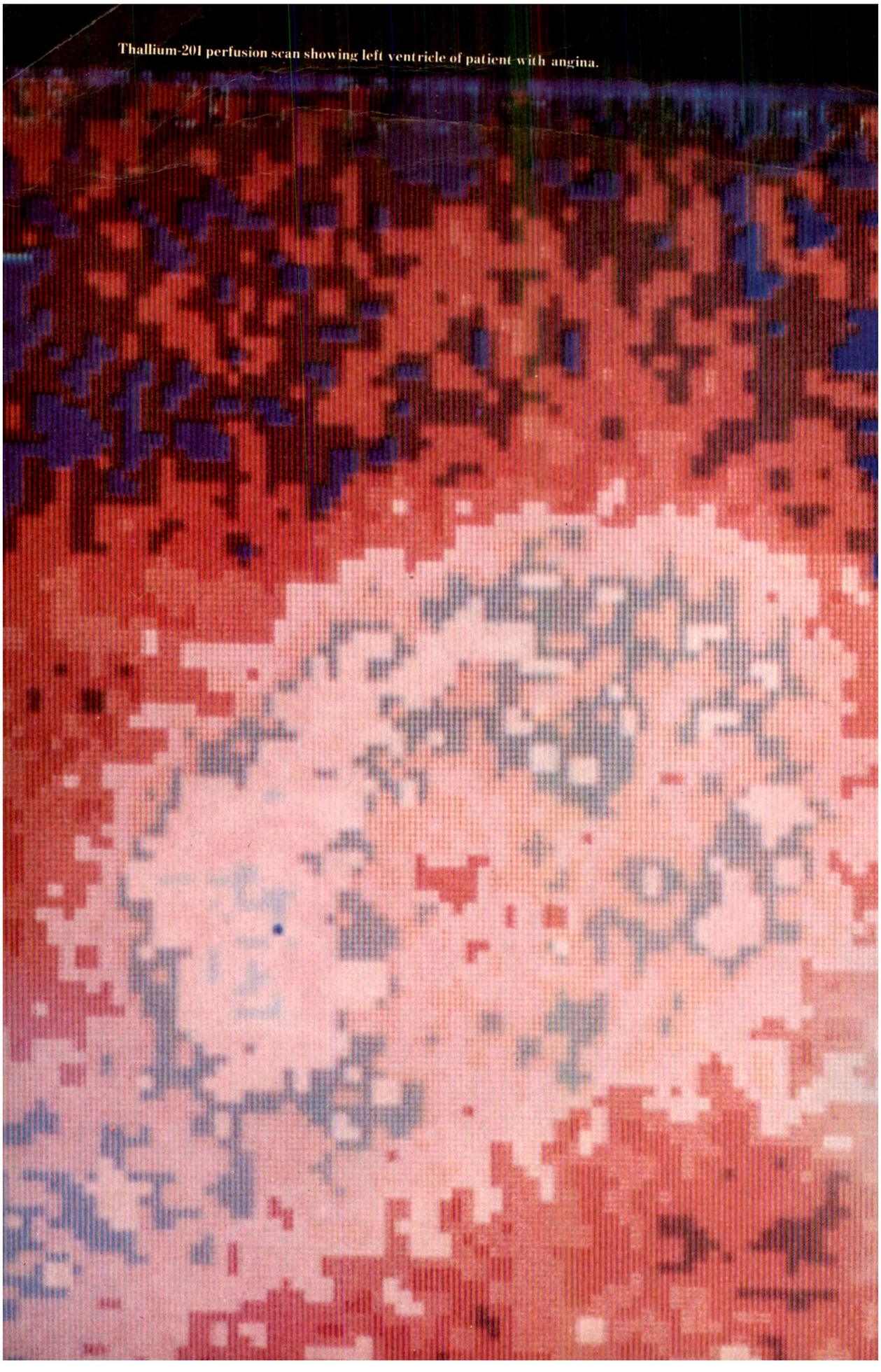

Thallium-201 perfusion scan showing left ventricle of patient with angina.

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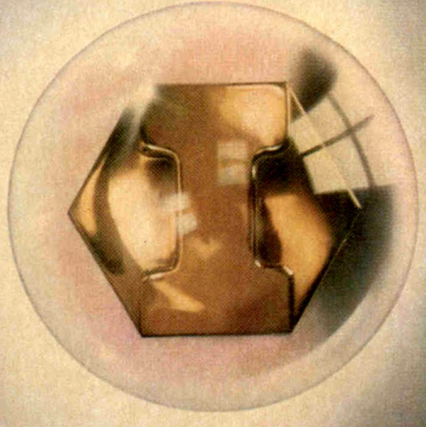

INDERAL®
(PROPRANOLOL HCl)

COMPREHENSIVE CARDIOVASCULAR PROTECTION

Please see next page for brief summary of prescribing information.

INDERAL®
(PROPRANOLOL HCl)

CORE THERAPY FOR ANGINA.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

Propranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block chodilation produced by endogenous and exogenous catecholamine stimulation o receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonito and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is e important to keep in mind in patients with labile diabetes. Hypoglycemic attacks ma accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not b established. Use of any drug in pregnancy or women of childbearing potential requ the possible risk to mother and/or fetus be weighed against the expected therapeu fit. Embryotoxic effects have been seen in animal studies at doses about 10 times th mum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be clos observed if propranolol is administered. The added catecholamine-blocking action drug may then produce an excessive reduction of the resting sympathetic nervous a Occasionally, the pharmacologic activity of propranolol may produce hypotension a marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotensio

As with any new drug given over prolonged periods, laboratory parameters shoul observed at regular intervals. The drug should be used with caution in patients with renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hy sion; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thromb nic purpura. *Central Nervous System:* lightheadedness; mental depression manifes insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome charac by disorientation for time and place, short term memory loss, emotional lability, slight clouded sensorium, and decreased performance on neuropsychometrics. *Gastroin* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, teric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and tory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrom cytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. mucocutaneous reactions involving the skin, serous membranes and conjunctivae r for a beta blocker (practolol) have not been conclusively associated with propranolo *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenas

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INDERAL (propranolol hydrochloride)

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Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

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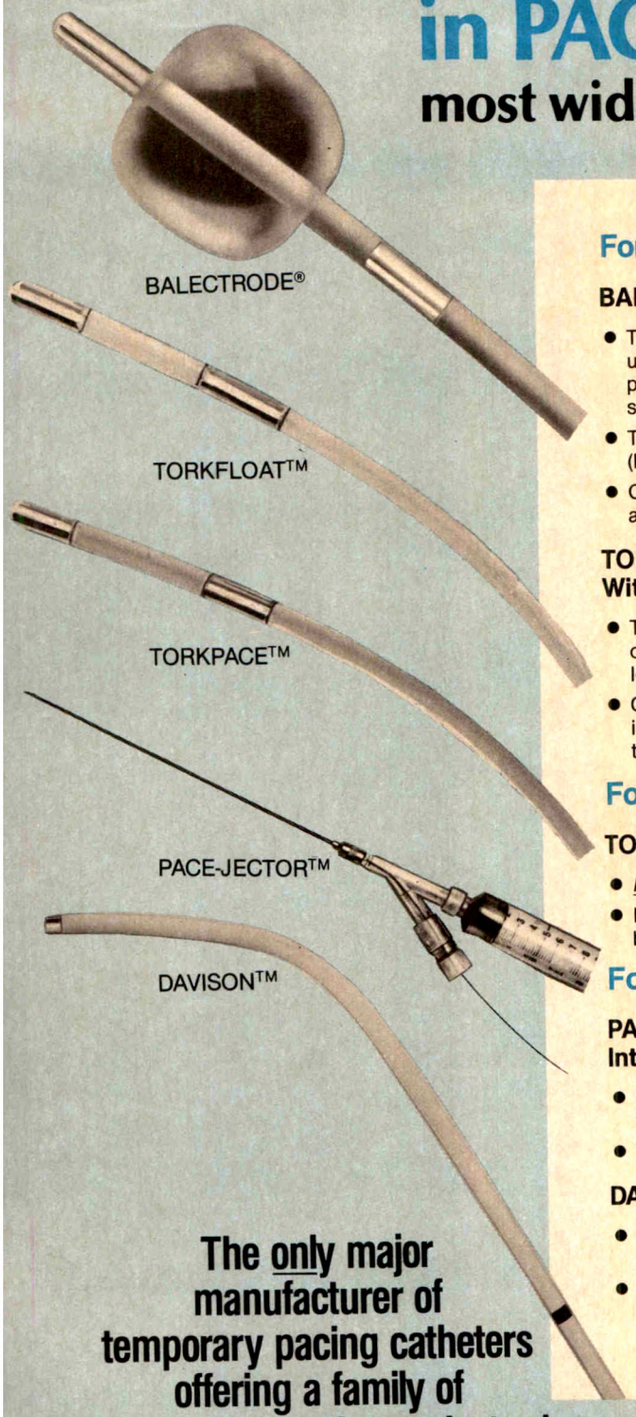

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In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this comoination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, light-headedness, and tremor; (3) G.I. symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at the rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

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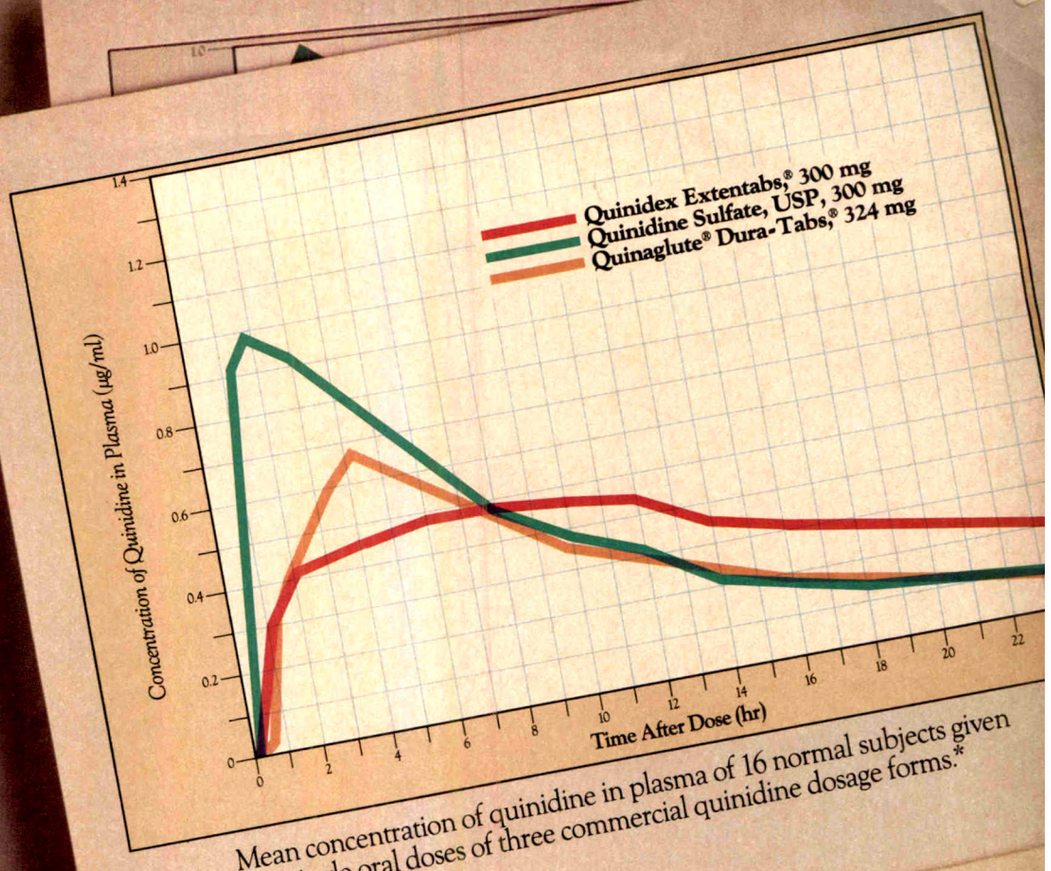

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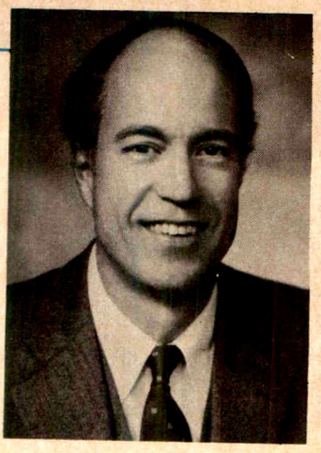


Oslerian Advice

In 1959 I purchased from Old Hickory Bookshop in Brinklow, Maryland, a book entitled *Sir William Osler, Bart., Brief Tributes to His Personality, Influence and Public Service Written by His Friends, Associates and Former Pupils, In Honor of His Seventieth Birthday and First Published in The Bulletin of The Johns Hopkins Hospital for July, 1919.* This 167-page book, which also contains Osler's bibliography, has since been a steady companion of mine. My favorite chapter was written by his former Johns Hopkins' Chief Resident, William S. Thayer, who described the third heart sound, and is entitled "Osler, The Teacher." In it, Thayer paraphrases comments of Osler apparently reiterated many times during rounds and other discussions. The comments are as appropriate 64 years later as when they were recorded by Thayer:

Observe, record, tabulate, communicate.

Use your five senses. The art of the practice of medicine is to be learned only by experience; 'tis not an inheritance; it cannot be revealed. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone can you become expert. Medicine is learned by the bedside and not in the classroom. Let not your conceptions of the manifestations of disease come from words heard in the lecture room or read from the book. See, and then reason and compare and control. But see first. No two eyes see the same thing. No two mirrors give forth the same reflection. Let the word be your slave and not your master.

Live in the ward. Do not waste the hours of daylight in listening to that which you may read by night. But when you have seen, read. And when you can, read the original descriptions of the masters who, with crude methods of study, saw so clearly.

Record that which you have seen; make a note at the time; do not wait. "The flighty purpose never is o'ertook, unless the deed go with it."

Memory plays strange pranks with facts. The rocks and fissures and gullies of the mountain-side melt quickly into the smooth, blue outlines of the distant panorama. Viewed through the perspective of memory, an unrecorded observation, the vital details long since lost, easily changes its countenance and sinks obediently into the frame fashioned by the fancy of the moment.

Always note and record the unusual. Keep and compare your observations. Communicate or publish short notes on anything that is striking or new. Do not waste your time in compilations, but when your observations are sufficient, do not let them die with you. Study them, tabulate them, seek the points of contact which may reveal the underlying law. Some things can be learned only by statistical comparison. If you have the good fortune to command a large clinic, remember that one of your chief duties is the tabulation and analysis of the carefully recorded experience.

The collection and study of your own observations is much, but he who works in his own small compartment leads, after all, a restricted and circumscribed life. Go out among your fellows, and learn of them. The good observer is not limited to the large hospital. The modest country doctor may furnish you the vital link in your chain, and the simple rural practitioner is often a very wise man.

Respect your colleagues. Know that there is no more high-minded body of men than the medical profession. Do not judge your confrères by the reports of patients, well meaning, perhaps, but often strangely and sadly misrepresenting. Never let your tongue say a slighting word of a colleage [sic]. It is not for you to judge. Let not your ear hear the sound of your voice raised in unkind criticism or ridicule or condemnation of a brother physician. If you do, you can never again meet that man face to face. Wait. Try to believe the best. Time will generally show that the words you might have spoken would have been unjust, would have injured a good man, and lost you a friend, and then—silence is a powerful weapon.

When you have made and recorded the unusual or original observation, or when you have accomplished a piece of research in laboratory or ward; do not be satisfied with a verbal communication at a medical society. Publish it. Place it on permanent record as a short, concise note. Such communications are always of value.

Mix with your colleagues; learn to know them. But in your relations with the profession and with the public, in everything that pertains to medicine, consider the virtues of taciturnity. Look out. Speak only when you have something to say. Commit yourself only when you can and must. And when you speak, assert only that of which you know. Beware of

words—they are dangerous things. They change color like the chameleon, and they return like a boomerang. Do you know the story of the young physician, about to enter practice, who was sent by his father to his old friend, Sir William Stokes, for advice? A pleasant conversation, and, at the doorway, a last word: "Charley, don't say too much." Then, at the gate, a voice: "Charley, come back a minute; I'm very fond of you, my boy; don't *do* too much."

"Don't do too much." Remember how much you do not know. Do not pour strange medicines into your patients. Our greatest assistance is given by simple physical and mental means, and by the careful employment of such drugs as have been adequately studied, with regard to the action of which we have real information. Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory from the careless mixing of unknown substances. Be as considerate of your patient and yourself as you are of the test-tube.

Familiarize yourself with the work of others and never fail to give credit to the precursor. Let every student have full recognition for his work. Never hide the work of others under your own name. Should your assistant make an important observation, let him publish it. Through your students and your disciples will come your greatest honor.

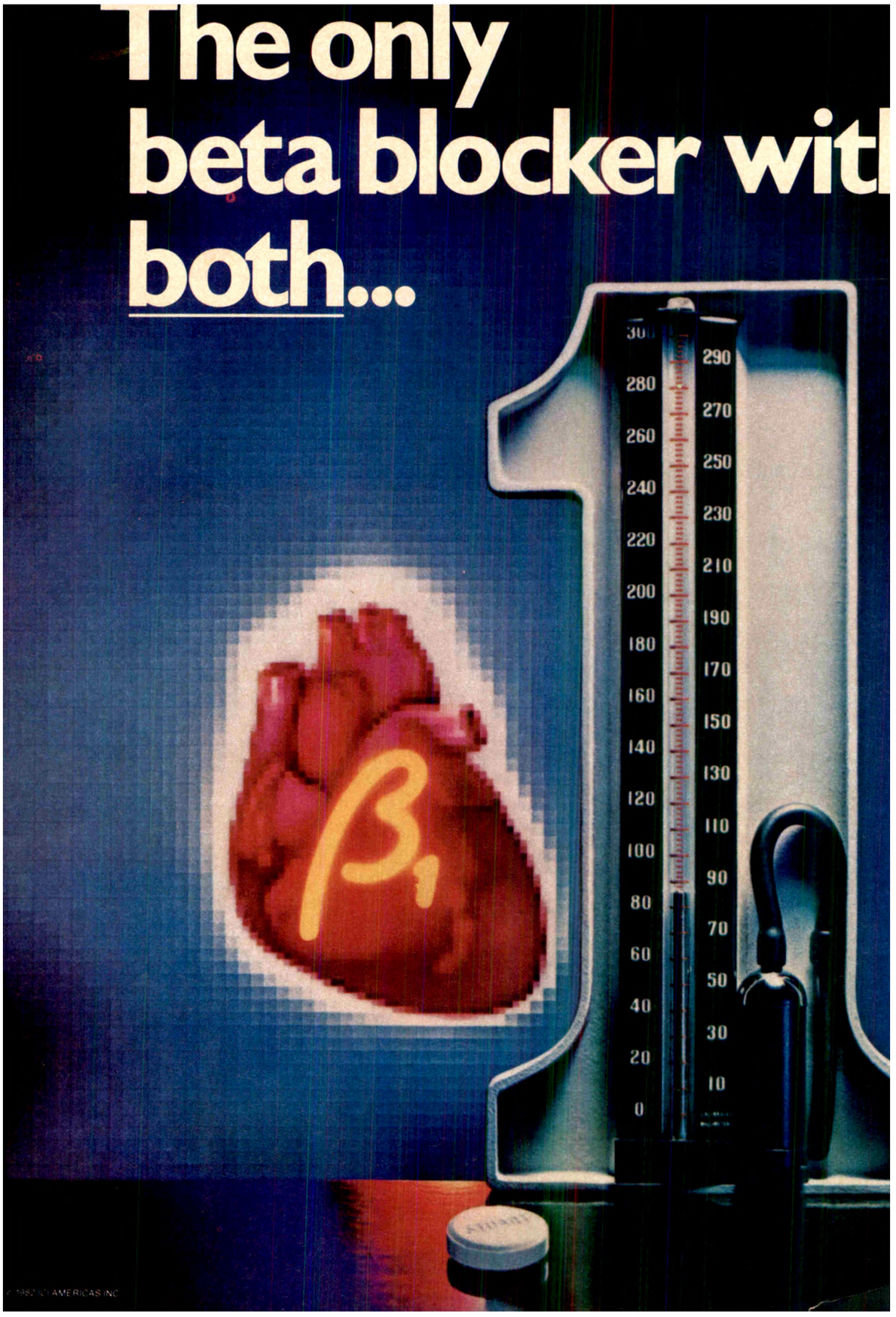
Be prompt at your appointments; that is always possible. Many are always late at a consultation; few miss a train. There is no excuse for tardiness.

Live a simple and a temperate life, that you may give all your powers to your profession. Medicine is a jealous mistress; she will be satisfied with no less.

Save the fleeting minute; do not stop by the way. Learn gracefully to dodge the bore. Strike first and quickly, and before he has recovered from the blow, be gone; 'tis the only way. . . .

If you can practice consistently all this, . . . and then, if you can bring into corridor and ward a light, springing step, a kindly glance, a bright word to every one you meet, arm passed within arm or thrown over the shoulder of the happy student or colleague; a quick, droll, epigrammatic question, observation or appellation that puts the patient at his ease or brings a pleased blush to the face of the nurse; an apprehension that grasps in a minute the kernel of the situation, and a memory teeming with instances and examples that throw light on the question; an unusual power of succinct statement and picturesque expression, exercised quietly, modestly and wholely without sensation; if you can bring into the lecture room an air of perfect simplicity and directness, and, behind it all, have an ever-ready store of the most apt and sometimes surprising interjections that so light up and emphasize that which you are setting forth that no one in the room can forget it; if you can enter the sick-room with a song and an epigram, an air of gaiety, an atmosphere that lifts the invalid instantly out of his ills, that produces in the waiting hypochondriac so pleasing a confusion of thought that the written list of questions and complaints, carefully compiled and treasured for the moment of the visit, is almost invariably forgotten; if the joy of your visit can make half a ward forget the symptoms that it *fancied* were important, until you are gone; if you can truly love your fellow, and, having said evil of no man, be loved by all; if you can select a wife with a heart as big as your own, whose generous welcome makes your tea-table a Mecca; . . . if you can do all this, you may begin to be to others the teacher that "the chief" is to us!

William C. Roberts, MD
Editor-in-Chief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See last page of this advertisement for brief summary of prescribing information.

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TENORMIN® (atenolol)

A beta$_1$-selective blocking agent for hypertension.

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

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CONTENTS

CONGENITAL HEART DISEASE

1469 Accuracy of 2-Dimensional Echocardiographic Diagnosis of Congenitally Bicuspid Aortic Valve: Echocardiographic-Anatomic Correlation in 115 Patients

ROBERT O. BRANDENBURG, Jr., ABDUL J. TAJIK, WILLIAM D. EDWARDS, GUY S. REEDER, CLARENCE SHUB, and JAMES B. SEWARD

In 115 patients under age 50 years who had 2-dimensional (2-D) echocardiographic examinations before aortic valve surgery at the Mayo Clinic, the echocardiograms were reviewed blindly, and the aortic valve structure was categorized as bicuspid, tricuspid, or indeterminate. On the basis of combined surgical and pathologic inspection, 50 aortic valves were congenitally bicuspid, 60 were tricuspid, 4 were unicommissural, and 1 was quadricuspid. By 2-D echocardiography, the number of cusps was indeterminate in 29 patients (25%). When these patients were excluded, the sensitivity, specificity, and diagnostic accuracy of 2-D echocardiography for bicuspid aortic valve were 78, 96, and 93%, respectively. Thus, with adequate 2-D images, echocardiography is a sensitive and highly specific technique for the diagnosis of bicuspid aortic valve.

1474 Classification of the Site of Ventricular Septal Defect by 2-Dimensional Echocardiography

HORACIO CAPELLI, JOSE L. ANDRADE, and JANE SOMERVILLE

Sixty-three patients with ventricular septal defect were investigated with 2-dimensional echocardiography to assess its accuracy in defining the anatomic site of the defect. The defects were classified into subvalvular (subdivided according to which valve the defect is related) and muscular (subdivided according to location in the muscular septum). Echocardiographic findings were compared with the surgical findings in all patients. The method proved reliable in identifying most of the defects and capable of replacing invasive investigation for assessment of uncomplicated ventricular septal defect before surgery.

1481 Results After Repair of Coarctation of the Aorta Beyond Infancy: A 10 to 28 Year Follow-Up With Particular Reference to Late Systemic Hypertension

PATRICIA M. CLARKSON, MICHAEL R. NICHOLSON, BRIAN G. BARRATT-BOYES, JOHN M. NEUTZE, and RALPH M. WHITLOCK

The late outcome in 160 patients aged 1 to 54 years who had surgical repair of coarctation of the aorta was examined 10 to 28 years postoperatively. The minimum duration of follow-up in survivors was 10 years. Twenty years postoperatively the probability of survival of patients discharged from the hospital aged 1 to 19 years at operation was a little less than that of the general population (95% versus 97%). The divergence of death rate from normal was increasingly more marked with increasing age at operation beyond 20 years. Hypertension was more common in patients operated on after age 20 years than in those aged 5 to 19 years at operation ($p = 0.007$). The likelihood of being alive without complications and with a normal blood pressure was 69% at 10 years, 55% at 15 years, and 20% at 25 years postoperatively.

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1489 The Valve of the Foramen Ovale in Interatrial Right-to-Left Shunt: Echocardiographic Cineangiocardiographic and Hemodynamic Observations

CHRISTOPH KUPFERSCHMID and DIETER LANG

The valve of the foramen ovale fails to close in patients with postpartum persistent interatrial right-to-left shunt, whether functional or dependent on a cardiac defect. Then it consistently has a marked movement within the cardiac cycle which occasionally can be seen on cineangiocardiography. On M-mode and 2-dimensional echocardiography this movement can be recorded frequently. In 13 patients with cyanotic heart disease and 11 newborns with persistent transatrial right-to-left shunt, the movement of the foramen ovale flap was studied echocardiographically and the findings were compared with those obtained in 20 healthy infants and children. Analysis of interatrial blood pressure differences in 2 patients revealed that the movement of the valve of the foramen ovale reflects interatrial pressure-flow dynamics.

1495 Management of Adults With Congenital Bidirectional Cardiac Shunts, Cyanosis, and Pulmonary Vascular Obstruction: Successful Operative Repair in 3 Patients

VERDI J. DISESA, LAWRENCE H. COHN, and WILLIAM GROSSMAN

Patients with congenital cardiac shunts in whom marked functional disability, cyanosis, and pulmonary hypertension develop have been considered inoperable or at exceedingly high risk. Three adult patients presented with New York Heart Association class IV symptoms, bidirectional shunting with cyanosis, polycythemia, severe pulmonary hypertension, and increased pulmonary vascular resistance. Pulmonary arterial pressure did not decrease in response to administration of 100% oxygen, and 2 patients had lung biopsy results showing advanced pulmonary vascular obstruction. However, in all patients, the net shunt was left-to-right ($Q_p/Q_s > 1$) and the resistance ratio (R_p/R_s) <0.5. All patients survived operation and are now in NYHA class I or II. At repeat cardiac catheterization, pulmonary arterial pressure and resistance had decreased substantially. This high-risk group of patients should still be considered for surgical correction if the usual criteria for operability exist: net left-to-right Q_p/Q_s and $R_p/R_s < 0.50$.

1498 Obstruction Within the Right Ventricular Body: Two-Dimensional Echocardiographic Features

LAURA J. von DOENHOFF and NAVIN C. NANDA

Real-time 2-dimensional echocardiograms were performed in 4 patients, all with considerable obstruction within the body of the right ventricle proven at cardiac catheterization and biplane ventriculography. In 3 patients, the obstruction presented echocardiographically as an "hourglass" narrowing within the right ventricle, and a membranous ventricular septal defect was also present. In the fourth, a patient with hypertrophic cardiomyopathy, the obstruction was seen as a bulging of the septum into the right ventricle. In 3 patients the obstruction was convincingly demonstrated only in the subcostal right ventricular inflow-apex-outflow plane, rather than in the standard echocardiographic planes. Obstruction within the body of the right ventricle is a potentially serious condition which has been overlooked both at cardiac catheterization and at surgery. Demonstration of this lesion by 2-dimensional echocardiography appears feasible and would greatly improve diagnostic accuracy.

1502 Quantitative Analysis of Pulmonary Vascular Disease in Simple Cardiac Anomalies With the Down Syndrome

SHIGEO YAMAKI, TOGO HORIUCHI, and YOSHIHITO SEKINO

Intimal changes and medial thickness of small pulmonary arteries were morphometrically examined in 21 cases of simple cardiac anomalies with the Down syndrome, and their correlations with age and with pulmonary arterial peak pressure were then compared with those of 20 cases of simple cardiac anomalies without the Down syndrome and 17 cases of complete transposition of the great arteries (TGA). Results indicate that (1) intimal changes developed at an earlier age in patients with simple cardiac anomalies and the Down syndrome than in those without the Down syndrome, (2) the intimal changes were more severe than those in simple cardiac anomalies without the Down syndrome at the same level of pulmonary arterial pressure and milder than those in TGA,

Continued on Page A18

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Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

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and (3) the media of small pulmonary arteries in simple cardiac anomalies with the Down syndrome was thinner than the media in cases without the syndrome at the same radius and the same level of pulmonary arterial pressure but thicker than the media in TGA.

1507 Two-Dimensional Echocardiographic Recognition of the Right Aortic Arch

VINCENZO CELANO, DANIEL R. PIERONI, ROBERT L. GINGELL, and J-MICHEL A. ROLAND

A mirror image right aortic arch (RAA) is frequently associated with congenital heart disease. While 2-dimensional (2-D) echocardiography has been used to elucidate the left aortic arch (LAA), detailed description of the technique for RAA has not been reported. This study was pursued to delineate the 2-D echocardiographic approach to the patient with RAA. There were 27 patients with LAA (Group A) and 27 with RAA (Group B) in this study. The standard suprasternal long axis correctly identified the LAA in all Group A patients, but in Group B it located only the ascending aorta. This simulated an interrupted aortic arch anomaly. Transducer realignment to position 2 confirmed RAA in all Group B patients. In the parasternal axes the left descending aorta was detected posterior to the atrioventricular groove or left ventricle in every Group A patient but in none in Group B. The descending aorta was found to the left of the spine on the abdominal short-axis view in both groups. The 2-D echocardiographic technique proposed for RAA is simple, rapid, and definitive. It should be pursued whenever LAA cannot be demonstrated, especially in children in whom a congenital heart defect is suspected. Anticipation of RAA can be used to expedite chest and cardiovascular surgery.

SYMPOSIUM ON RESULTS OF THE MUSTARD OPERATION FOR COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

JAMES R. ZUBERBUHLER, Guest Editor

1513 Introduction

JAMES R. ZUBERBUHLER

1514 Hemodynamic Function After the Mustard Operation for Transposition of the Great Arteries

SANG C. PARK, WILLIAM H. NECHES, ROBERT A. MATHEWS, FREDERICK J. FRICKER, LEE B. BEERMAN, DONALD R. FISCHER, CORA C. LENOX, and JAMES R. ZUBERBUHLER

Pre- and postoperative cardiac catheterization data and cineangiograms were reviewed in 82 patients surviving the Mustard operation for transposition of the great arteries. Forty-six (56%) had no or insignificant associated cardiac lesions, while the remaining 36 had a ventricular septal defect, pulmonic stenosis, or both, requiring surgical intervention at the time of operation. Significant systemic venous obstruction occurred in 11 patients (13%), and 6 of these 11 required reoperation. Superior vena caval obstruction was well tolerated in most patients, even when there was high pressure in the superior vena cava. Pulmonary venous obstruction was a less common complication, occurring in 5 patients. Tricuspid regurgitation was uncommon but occurred more often in patients who had transatrial closure of a ventricular septal defect. Left ventricular outflow obstruction was common (38%) preoperatively. The obstruction was relieved surgically in 12 patients, and 6 of these patients with localized obstruction had a good result. However, the gradient was not adequately relieved in patients with diffuse obstruction. Mild to moderate left ventricular outflow gradients regressed spontaneously in most patients after the Mustard operation.

1520 Rest and Exercise Right and Left Ventricular Function Late After the Mustard Operation: Assessment by Radionuclide Ventriculography

JUDITH H. MURPHY, MARTHA M. BARLAI-KOVACH, ROBERT A. MATHEWS, LEE B. BEERMAN, SANG C. PARK, WILLIAM H. NECHES, and JAMES R. ZUBERBUHLER

Rest and exercise radionuclide ventriculography was performed in 26 asymptomatic patients with transposition of the great arteries a mean of 9.3 years after they underwent the Mustard operation. The mean resting right (systemic) ventricular ejection fraction (RVEF) was 0.50 ± 0.10 (±1 standard deviation). With exercise the RVEF increased in 9 patients and either failed to increase or decreased in 15. The weight-adjusted work load performed

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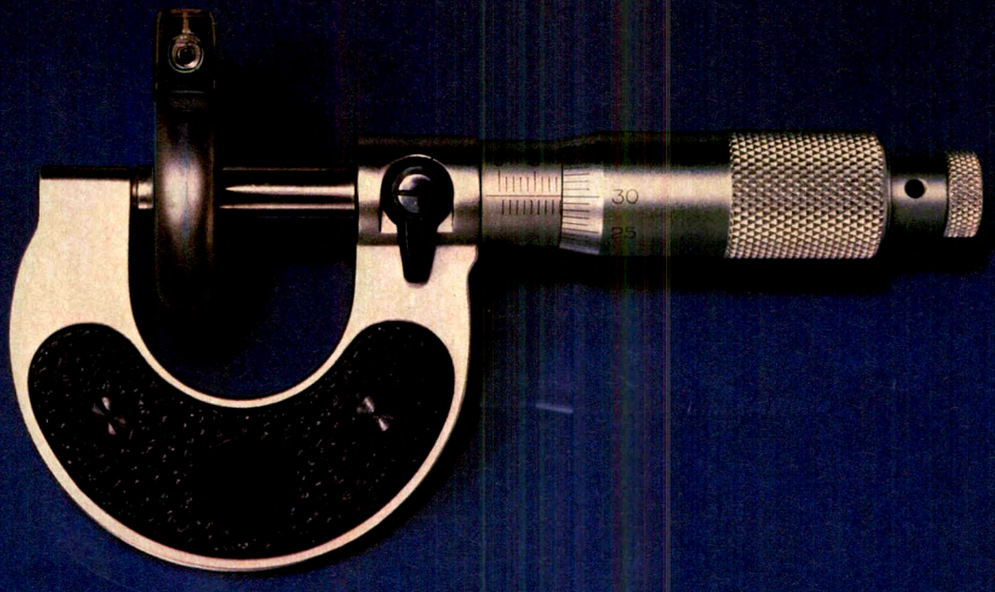

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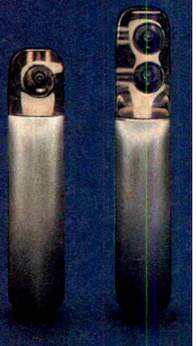

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was a first predictor of right ventricular exercise response; patients whose RVEF increased did more work. The mean resting left (pulmonic) ventricular ejection fraction (LVEF) was 0.58 ± 0.09. With exercise LVEF increased in 14 patients and failed to increase in 10. The presence of complex ventricular arrhythmia documented on Holter monitoring was a first predictor of failure of the LVEF to increase with exercise. No other factors were predictive of the rest or exercise ejection fraction of either ventricle.

26 Exercise Studies After the Mustard Operation in Transposition of the Great Arteries

ROBERT A. MATHEWS, FREDERICK J. FRICKER, LEE B. BEERMAN, ROBERT J. STEPHENSON, DONALD R. FISCHER, WILLIAM H. NECHES, SANG C. PARK, CORA C. LENOX, and JAMES R. ZUBERBUHLER

Twenty-one postoperative patients with transposition of the great arteries (TGA) underwent graded exercise testing 4 to 15 years (mean 9) after the Mustard operation. No patients had subject exercise intolerance before testing, although some had symptomatic resting arrhythmias. Correlations were made between cardiac catheterization data and 24-hour ambulatory monitoring. Exercise tolerance was diminished in nearly half of the patients. No statistically significant differences were found in heart rate or blood pressure responses, but maximal oxygen consumption values were lower than the control values ($p < 0.001$) in the larger patients. Arrhythmias were present or provoked in most patients during exercise testing. Only 28% remained in normal sinus rhythm during and after exercise. Multifocal premature contractions were the most serious arrhythmias demonstrated. Some long-term survivors of the Mustard operation may have abnormal exercise dynamics, even though they may be asymptomatic and have normal physical activities and endurance. Mean maximal systolic blood pressure, heart rate, oxygen consumption, and maximal treadmill times were consistently in the low-normal range or were statistically lower than normal.

0 Arrhythmias in Transposition of the Great Arteries After the Mustard Operation

LEE B. BEERMAN, WILLIAM H. NECHES, FREDERICK J. FRICKER, ROBERT A. MATHEWS, DONALD R. FISCHER, SANG C. PARK, CORA C. LENOX, and JAMES R. ZUBERBUHLER

The purpose of this study was to provide a systematic evaluation of the electrophysiologic function of 87 survivors of the Mustard operation at a single institution. The review of the surface electrocardiograms showed normal sinus rhythm in 52%, sinus node dysfunction in 27%, and atrioventricular block in 16%. Holter monitoring was performed in an unselected subgroup of 26 patients. Sinus node dysfunction was found in 58%, atrioventricular block in 27%, ventricular ectopy in 50%, and supraventricular ectopy in 27%, and only 8% had no abnormalities present. Intracardiac electrophysiologic evaluation showed a high incidence of abnormal sinus node recovery times and suboptimal response of the atrioventricular conduction system to rapid atrial pacing. When all the modalities used in this study were considered, sinus node dysfunction occurred in 47% of patients, ectopy in 34%, and atrioventricular block in 23%. Although only 30% of the group had no evidence of dysrhythmias, symptoms from rhythm or conduction disturbances were uncommon.

Summary

JAMES R. ZUBERBUHLER

VALVULAR HEART DISEASE

Trial of Combined Warfarin Plus Dipyridamole or Aspirin Therapy in Prosthetic Heart Valve Replacement: Danger of Aspirin Compared With Dipyridamole

JAMES H. CHESEBRO, VALENTIN FUSTER, LILA R. ELVEBACK, DWIGHT C. McGOON, JAMES R. PLUTH, FRANCISCO J. PUGA, ROBERT B. WALLACE, GORDON K. DANIELSON, THOMAS A. ORSZULAK, JEFFREY M. PIEHLER, and HARTZELL V. SCHAFF

The incidence of thromboembolism in patients with prosthetic heart valves increases directly with time after operation. Patients with 1 or more mechanical prosthetic heart valves were randomized to therapy with warfarin plus dipyridamole (400 mg/day) or warfarin plus aspirin (500 mg/day) and followed with a concurrent nonrandomized control group taking warfarin alone. In 534 patients followed up 1,319 patient-years, excessive bleed-

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ing requiring blood transfusion, or hospitalization occurred in more patients on warfarin plus aspirin (23 of 170 [14%], or 6.0/100 patient-years) than in patients on warfarin plus dipyridamole (7 of 181 [4%], or 1.6/100 patient years, $p < 0.001$) or warfarin alone (9 or 183 [5%], or 1.8, $p < 0.001$). A trend toward reduction in thromboembolism was present in the warfarin plus dipyridamole group (2 of 181 [1%], or 0.5/100 patient-years) compared with warfarin plus aspirin (7 of 170, 4%, or 1.8/100 patient-years) or warfarin alone (6 of 183, 4%, or 1.2/100 patient-years). Warfarin plus aspirin resulted in excessive bleeding and is contraindicated. Continued follow-up is in progress for the detection of thromboembolism.

1542 Early Detection of Left Ventricular Dysfunction in Chronic Aortic Regurgitation as Assessed by Contrast Angiography, Echocardiography, and Rest and Exercise Scintigraphy

ROBERT L. HUXLEY, ANDREW GAFFNEY, JAMES R. CORBETT, BRIAN G. FIRTH, RONALD PESHOCK, PASCAL NICOD, JAMES S. RELLAS, GEORGE CURRY, SAMUEL E. LEWIS, and JAMES T. WILLERSON

The best method for detecting early left ventricular (LV) dysfunction in patients with chronic aortic regurgitation (AR) is uncertain. Variables used previously to identify dysfunction have included (1) angiographic methods to identify an LV end-systolic volume index (LVESVI) ≥ 60 ml/m^2, (2) echocardiographic measurements to identify LV end-systolic dimension (LVESD) ≥ 5.5 cm or LV fractional shortening $\leq 25\%$, and (3) a depressed LV ejection fraction (EF) at rest and/or an LVEF or LVESVI that deteriorates with exercise as detected by myocardial scintigraphic measurements. In the present study, 15 consecutive asymptomatic or only mildly symptomatic patients with isolated 2+ to 4+ AR underwent (1) rest and exercise gated radionuclide ventriculography, (2) M-mode echocardiography, and (3) LV angiography. No other cause of LV dysfunction was apparent in 13 patients; 1 patient had moderate systemic arterial hypertension and 1 had 50% luminal diameter narrowing of the proximal left anterior descending coronary artery. Ten patients had abnormal LV function during exercise as evidenced by radionuclide ventriculography. However, only 4 of the 10 patients with exercise-induced LV dysfunction had an angiographic left ventricular end-systolic index ≥ 60 ml/m^2, and only 1 had an echocardiographically determined LVESD ≥ 5.5 cm. Thus (1) exercise radionuclide ventriculography identifies LV dysfunction earlier than traditionally used measurements, (2) LV dysfunction appears to persist in patients who manifest it and develop in others who did not have it originally, and (3) echocardiographic dilatation of the LVESD to ≥ 5.5 cm appears to be a late and relatively unusual occurrence.

1551 Effect of Elevating the Wrist on the Radial Pulse in Aortic Regurgitation: Corrigan Revisited

CAROLE A. WARNES, PETER C. HARRIS, and HARRY W. FRITTS

In 5 patients with severe aortic regurgitation (AR), the intraarterial radial pulse was recorded simultaneously with the external radial artery deflection of the other wrist. Recordings were made with the arms horizontal and repeated after elevation of the wrists, until the arms were vertical. Elevating the arm of a patient with AR increased the pulsation recorded over the radial artery, lowered the mean intraarterial pressure, and reduced the pulse pressure. The results suggest that elevation increases the compliance of the arterial wall, primarily by moving the artery to a lower position on its pressure-volume curve. The same changes occurred in 5 normal subjects but were less pronounced.

THERAPY

1554 Effects of Disopyramide on Left Ventricular Function: Assessment by Radionuclide Cineangiography

JOHN GOTTDIENER, ROBERT DIBIANCO, RICHARD BATES, BERTRAM J. SAUBERBRUNN, and ROSS D. FLETCHER, *With the technical assistance of* ROD NOSS and ANN RUSK

Disopyramide, although an effective antiarrhythmic drug, has been associated with congestive heart failure. Therefore, radionuclide cineangiography was performed at rest and during exercise stress to determine the effects of disopyramide on left ventricular function in patients with coronary artery disease and idiopathic dilated cardiomyopathy. An oral loading dose of 300 mg (serum level 3.6 ± 1.3 μg/ml) produced significant decreases in ejection fraction at rest and during exercise in most patients, whereas a smaller maintenance dose of 150 mg 4 times daily did not. Such "loading" regimens or any chronic drug regimen associated with similarly high, albeit "therapeutic" drug levels should be monitored closely.

Continued on Page A27

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the impressive clinical data[1] that documented t
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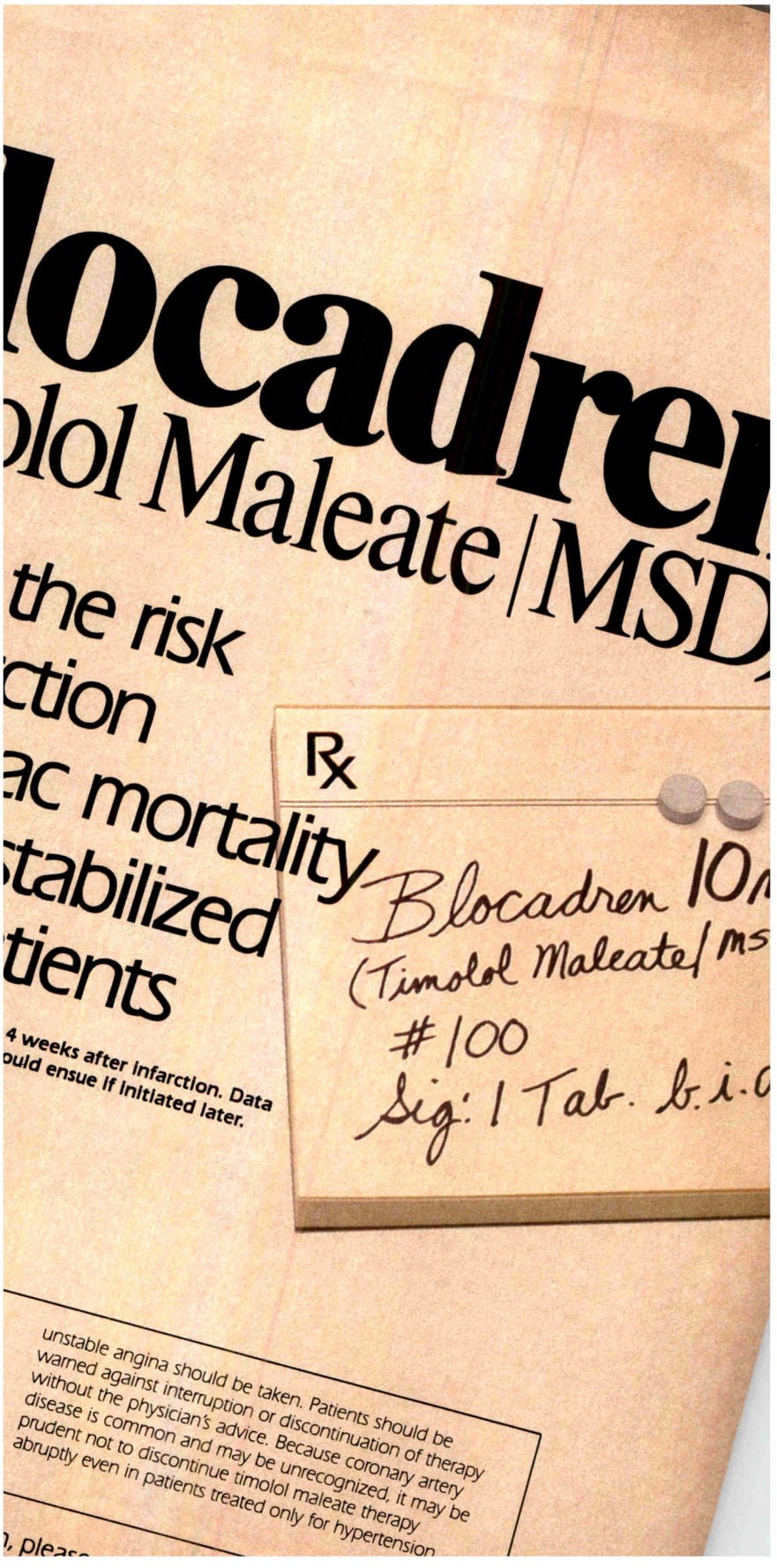
stabilized patients who have survived
the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduct
and reinfarction in patients surviving acute myocardial infarction,
304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.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unstable angina should be taken. Patients should be
warned against interruption or discontinuation of therapy
without the physician's advice. Because coronary artery
disease is common and may be unrecognized, it may be
prudent not to discontinue timolol maleate therapy
abruptly even in patients treated only for hypertension

(TIMOLOL MALEATE) MSD

CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

MSD Enquire detailed information overleaf

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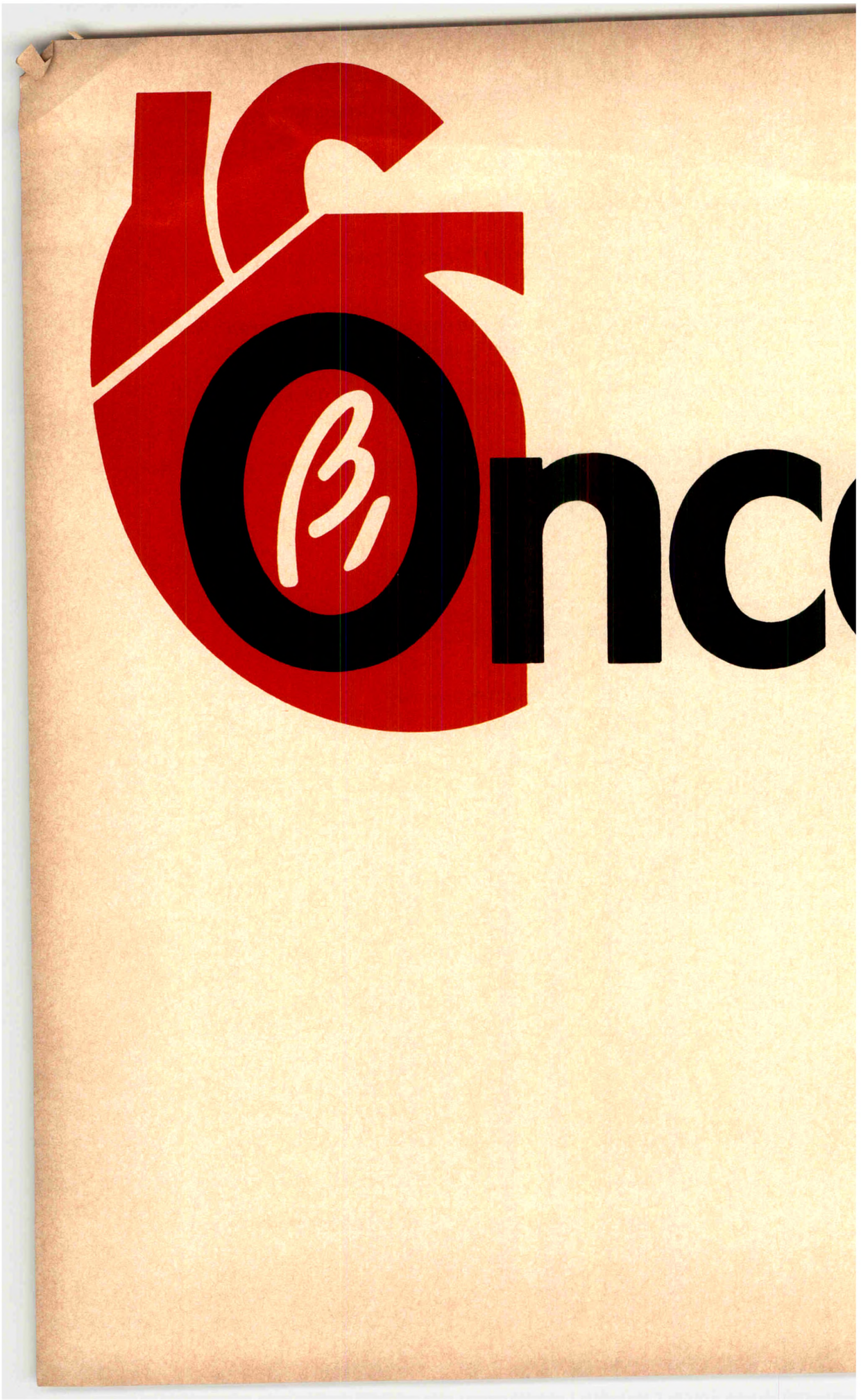
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Lower doses (especially 100 mg) may not maintain full effect at end of 24-hour period. Measure BP near end of dosing interval, adjust to larger or more frequent dosage if needed.

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Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

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metoprolol tartrate

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Prescribing Information

Brief Summary of Prescribing Information.

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings *Cardiac Failure:* Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions *Impaired Hepatic or Renal Function:* The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

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The oculomucocutaneous syndrom with the beta blocker practolol has with Lopressor during investigation eign marketing experience.

Potential Adverse Effects: In addi adverse effects not listed above hav with other beta-adrenergic blockin should be considered potential adv metoprolol.

Central Nervous System: Reversib sion progressing to catatonia; visu hallucinations; an acute reversible acterized by disorientation for time term memory loss, emotional labilit sensorium, and decreased perform neuropsychometrics.

Cardiovascular: Intensification of A **Contraindications**).

Hematologic: Agranulocytosis, no penic purpura, thrombocytopenic p

Allergic: Erythematous rash, fever aching and sore throat, laryngospa tory distress.

Miscellaneous: Reversible alopeci

Clinical Laboratory Test Findings: urea levels in patients with severe elevated serum transaminase, alk phatase, lactate dehydrogenase.

Dosage and Administration Dos should be individualized. The usua 100 mg daily in single or divided do alone or added to a diuretic. The d increased at weekly (or longer) int timum blood pressure reduction is general, the maximum effect of an level will be apparent after one we effective dosage range is 100 to 45 Dosages above 450 mg per day ha ied. While once daily dosing is effe maintain a reduction in blood pres the day, lower doses (especially 10 maintain a full effect at the end of t and larger or more frequent daily d quired. This can be evaluated by m pressure near the end of the dosin mine whether satisfactory control i tained throughout the day. Beta$_1$ s ishes as dosage of Lopressor is in

This drug should be stored at cont perature and protected from moist

How Supplied Tablets of 50 mg (c scored, light red, film-coated) and shaped, scored, light blue, film-co in bottles of 100 and 1,000 and Uni of 100.

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CONGENITAL HEART DISEASE

Accuracy of 2-Dimensional Echocardiographic Diagnosis of Congenitally Bicuspid Aortic Valve: Echocardiographic-Anatomic Correlation in 115 Patients

ROBERT O. BRANDENBURG, Jr., MD, ABDUL J. TAJIK, MD, WILLIAM D. EDWARDS, MD, GUY S. REEDER, MD, CLARENCE SHUB, MD, and JAMES B. SEWARD, MD

The preoperative 2-dimensional (2-D) echocardiograms of all patients <50 years of age in whom the aortic valve had been directly inspected by the surgeon or the pathologist or both were reviewed. From June 1977 to June 1981, 283 patients aged ≤50 years had aortic valve surgery at the Mayo Clinic: 115 (aged 1 to 50 years [mean 32]) had 2-D examinations preoperatively. The echocardiograms were reviewed blindly, and the aortic valve structure was categorized as bicuspid, tricuspid, or indeterminate. On the basis of combined surgical and pathologic inspection, 50 aortic valves were c genitally bicuspid, 60 were tricuspid, 4 were commissural, and 1 was quadricuspid. By echocardiography, the number of cusps was in terminate in 29 patients (25%). When these patie were excluded, the sensitivity, specificity, and agnostic accuracy of 2-D echocardiography for cuspid aortic valve were 78, 96, and 93%, resp tively. Thus, with adequate 2-D images, echoc diography is a sensitive and highly specific te nique for the diagnosis of bicuspid aortic valve

Bicuspid aortic valve is one of the most common congenital cardiac anomalies, occurring in 0.4 to 2% of all births. The most common complication is acquired stenosis due to calcification, with increased cuspid rigidity.[1,2] Infective endocarditis is a common cause of death in patients older than 20 years with bicuspid valve[3] and is potentially preventable with antibiotic prophylaxis. Because the complications of congenitally bicuspid aortic valve are potentially so devastating, its early identification is important. Although 2-dimensional (2-D) echocardiography has been used in the noninvasive diagnosis of bicuspid aortic valve, the agnostic accuracy of this technique is not establis This study determines the sensitivity, specificity, predictive accuracy of 2-D echocardiography in th agnosis of congenitally bicuspid aortic valve.

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Methods

Selection of patients: From June 1977 to June 1981 patients aged ≤50 years were operated on for aortic ste or aortic regurgitation. Preoperative 2-D echocardiogra examinations were performed in 115 of the 283 patients (4 These 115 patients form the basis of this retrospe study.

Patient population: There were 83 male and 32 fe patients aged 2 months to 50 years (mean 32 years). Tw patients had aortic valvotomy, and the remaining 103 pat had valve replacement. On clinical examination, 53 pat had isolated aortic regurgitation, 32 had isolated aortic

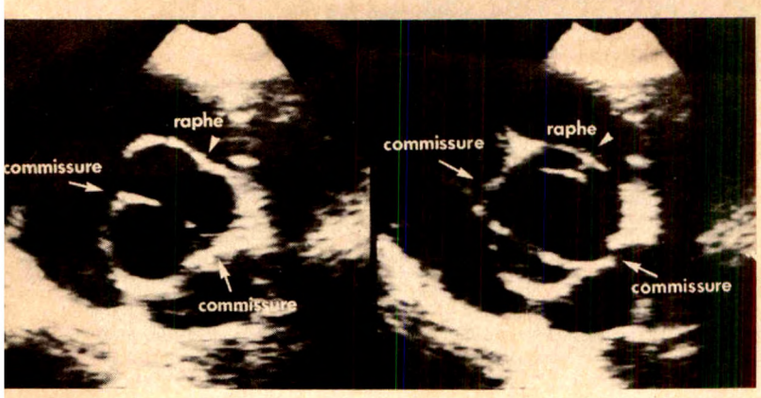

FIGURE 1. Parasternal short-axis view of a bicuspid aortic valve in diastole (**left**) and systole (**right**). Commissures are abnormally located at 4 o'clock and nearly 10 o'clock, with a raphe at 1 o'clock (**arrowhead**). Study of the valve's opening and closing pattern allows distinction of 2 rather than 3 cusps.

nosis, and 30 had combined aortic stenosis and aortic regurgitation. Seven patients had ascending aortic aneurysms (4 with Marfan's syndrome), and aortic dissections were present in 4 patients (2 with Marfan's syndrome). Seventeen patients (mean age 26 years; range 13 to 50) had a history of infective endocarditis: 15 of them had isolated aortic regurgitation, and 2 had combined aortic regurgitation and aortic stenosis.

Echocardiographic examination: *M-mode:* M-mode echocardiograms were obtained in 84 (73%) of 115 patients and were reviewed blindly to determine the eccentricity index. Eccentricity index of the diastolic aortic valve echoes was calculated according to the following formula: EI = 0.5 × A/a, where EI = eccentricity index, A = aortic root diameter at the onset of diastole, and a = distance from diastolic aortic closure to the nearest aortic wall at the onset of diastole.

Two-dimensional: Detailed 2-D echocardiographic examinations by a technique previously reported[4] were performed with a commercially available wide-angle phased-array or mechanical sector scanner (2.25-, 3-, or 5-MHz transducer). The images were permanently recorded on a 3/4-inch videotape for future analysis. Still frames of the sector scans published in this article were photographed by a 35-mm camera

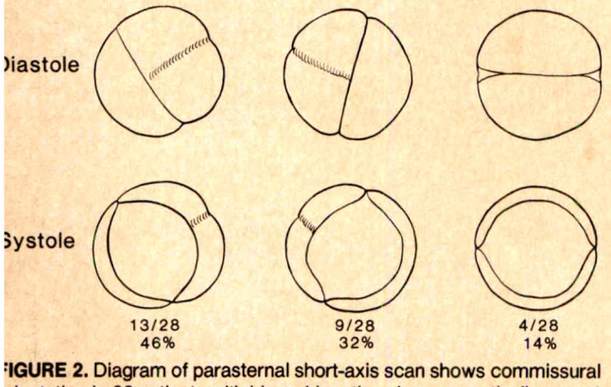

FIGURE 2. Diagram of parasternal short-axis scan shows commissural orientation in 28 patients with bicuspid aortic valves correctly diagnosed by 2-D echocardiography. Orientation of commissures was indeterminate in 2 patients. The most common pattern (**left pair**) demonstrated posterior commissure at the 4 or 5 o'clock position and anterior commissure at the 9 or 10 o'clock position, with raphe (when visualized) at the 1 or 2 o'clock position. This pattern resulted in a larger anterior and slightly smaller posterior cusp. In the next most common pattern (**middle pair**), anterior commissure was at the 1 or 2 o'clock position and posterior commissure usually at the 6 o'clock position, with raphe (when visualized) at the 9 or 10 o'clock position. This pattern usually resulted in a larger right than left cusp. Least frequently visualized (**right pair**) were commissures at the 3 and 9 o'clock positions (no raphe) resulting in equal-sized anterior and posterior cusps.

assembly. A satisfactory 2-D echocardiographic parasternal short-axis view was required to determine the number of aortic valve cusps with transducer angulation such that the aortic root appeared circular and not elliptical. Inaccurate angulation causes an oblique cut that makes valve cusps of equal size appear unequal and eccentric.

The 2-D echocardiographic examinations of the aortic valve in the long and, particularly, the short axes were reviewed blindly by 2 of us without knowledge of clinical information or surgical findings. Review of the videotapes was supplemented by the use of stop-frame and slow-motion analysis to enhance definition of rapidly moving cusps. In diastole, the normal aortic cusp margins form a Y pattern, with commissures at 2, 6, and 10 o'clock. Aortic valve commissures seen at other than these locations strongly suggested the presence of an anatomically abnormal and possibly bicuspid valve. Figure 1 shows a bicuspid valve with commissures at 4 and 10 o'clock and a raphe at 1 o'clock. We found 3 types of commissural orientation in bicuspid valves (Fig. 2). Special attention was also paid to the opening motion of the aortic cusps during systole, because this feature enhanced further the differentiation of a bicuspid from a tricuspid aortic valve (Fig. 3). On the basis of the foregoing criteria, the aortic valve was judged tricuspid, bicuspid, or indeterminate.

Surgical examination: A surgical description of the number of aortic valve cusps was available in 105 of the 115 patients (91%) but not in the remaining 10 patients. After excision, the valves were submitted for pathologic evaluation.

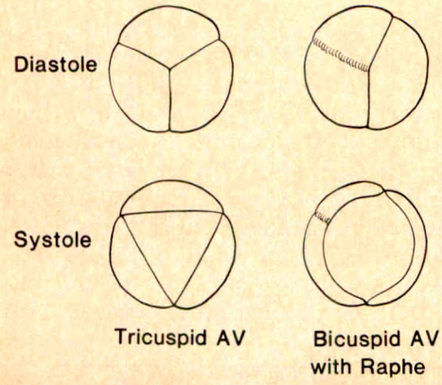

FIGURE 3. Diagram of parasternal short-axis scan of tricuspid (**left**) and bicuspid (**right**) aortic valves (AV) in diastole (**top**) and systole (**bottom**). Although diastolic appearance of both valves may be similar, viewing the opening pattern distinguishes a raphe from a commissure.

TABLE I Two-Dimensional Echocardiography in Aortic Valve Disease: Diagnosis in 115 Patients

Aortic Valve Structure	Patients	
	n	%
Bicuspid	31	27
Tricuspid	55	48
Indeterminate	29	25
Calcified valve	14	. . .
Inadequate visualization	15	. . .

Morphologic examination: Of the 103 aortic valves surgically excised at the time of aortic valve replacement, 10 from patients with a history of infective endocarditis were submitted for bacteriologic culture. Four valves were unavailable for pathologic examination, and 3 others were submitted in fragments, so that the number of cusps could not be determined. Therefore, pathologic analysis of the aortic valve was possible in 86 patients. In the remaining 29 patients, the number of aortic valve cusps was based solely on the surgeon's description. Anatomic correlation by surgical description or pathologic examination, or both, was available in all patients.

Results

Surgical-pathologic diagnosis: On the basis of combined surgical-pathologic evaluation, there were 50 congenitally bicuspid and 60 tricuspid aortic valves. Four patients had unicommissural valves, and 1 patient had a quadricuspid valve. Of the 86 valves examined pathologically, 82 had a surgical description available. Disagreement between surgical and pathologic diagnoses was noted in 6 patients (7%), and in all 6, a congenitally bicuspid valve (pathologic diagnosis) was called tricuspid by the surgeon. In these cases, the pathologic diagnosis was considered to be correct. Three unicommissural valves were diagnosed as bicuspid by the surgeon. The quadricuspid valve was correctly diagnosed at surgery. As noted, 29 valves had only a surgical description without pathologic confirmation.

Two-dimensional echocardiographic diagnosis: The number of aortic valve cusps could be determined by 2-D echocardiography in 86 patients (75%). Cusp number was indeterminate in the remaining 29 patients (25%)—in 15 (13%) because of inadequate echocardiographic imaging and in 14 (11%) because of extensive valvular calcification (Table I). Echocardiographic images were defined as inadequate when commissural margins and cuspid motion were indistinct without excessive valvular calcification or the tomographic section of aorta was not circular-appearing.

TABLE II Correlation Between Surgical-Pathologic Diagnosis and 2-D Echocardiographic Diagnosis in 85 Patients

Aortic Valve Structure by 2-D Echocardiography	Surgical-Pathologic Diagnosis of Aortic Valve Cusp Number	
	Bicuspid	Tricuspid
Bicuspid	28	2
Tricuspid	8	47
Diagnostic accuracy for		
Bicuspid valve	93%	
Tricuspid valve	85%	
Sensitivity	78%	
Specificity	96%	

Correlations between the surgical-pathologic and 2-D echocardiographic diagnoses were made after the 29 patients with indeterminate studies were excluded. A 2-D echocardiographic diagnosis of bicuspid aortic valve was made in 30 patients and was correct in 28 (93% diagnostic accuracy). Of 55 tricuspid valves, 47 were correctly diagnosed (85% diagnostic accuracy). Of the 36 bicuspid aortic valves (by surgical-pathologic examination), 28 were correctly diagnosed by 2-D echocardiography (78% sensitivity). Of 49 tricuspid valves (surgical-pathologic examination), 47 were correctly diagnosed by echocardiography (96% specificity) (Table II).

In 26 of the 28 patients with bicuspid aortic valves who had a correct 2-D echocardiographic diagnosis, the orientation of commissures was visualized (Fig. 2). Raphes were identified in 20 patients.

The accuracy of 2-D echocardiography in the diagnosis of a bicuspid aortic valve was not related to age of the patient, although the small numbers involved made analysis difficult (Table III). Both patients with tricuspid aortic valves and false-positive 2-D echocar-

TABLE III Accuracy of 2-D Echocardiographic Diagnosis Related to Age in 101 Patients*

Age (yr)	2-D Echocardiographic Diagnosis							
	Correct		Incorrect		Inadequate			
					Calcified		Incomplete	
	Tri	Bi	Tri	Bi	Tri	Bi	Tri	Bi
0–9	1	3	0	1	0	0	0	1
10–19	5	7	2	2	0	0	0	2
20–29	8	0	0	1	0	0	2	1
30–39	11	4	0	1	1	1	2	1
40–50	21	5	0	3	4	6	3	2

* Quadricuspid valve not included.
Bi = bicuspid aortic valve; Tri = tricuspid aortic valve.

TABLE IV Accuracy of 2-D Echocardiographic Diagnosis in 63 Patients With Aortic Regurgitation or Aortic Stenosis

2-D Echocardiographic Diagnosis	Surgical-Pathologic Diagnosis	
	Bicuspid	Tricuspid
Aortic regurgitation		
Bicuspid	11	1
Tricuspid	2	29
Aortic stenosis		
Bicuspid	10	1
Tricuspid	5	4
	Aortic	
	Insufficiency (%)	Stenosis (%)
Indeterminate study	17	31
Sensitivity	85	67
Specificity	97	80

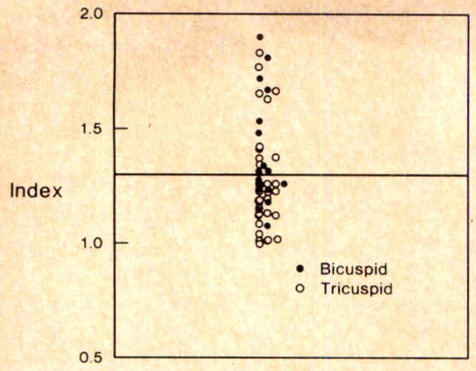

FIGURE 4. Preoperative M-mode eccentricity indexes in 54 patients. Horizontal line is drawn at eccentricity index 1.3.

diographic diagnoses of bicuspid aortic valve were young (aged 19 and 13). Pathologic confirmation was not available because both patients underwent aortic valvotomy.

Analysis of 2-D echocardiographic diagnostic accuracy related to the patient's functional lesion is shown in Table IV. Although the finding was not statistically significant, patients with aortic regurgitation had a correct diagnosis more often than did patients with isolated aortic stenosis (sensitivity 85 and 67%, respectively) ($p = 0.40$). The specificity for the diagnosis of tricuspid aortic valve was also higher in patients with aortic regurgitation than in those with aortic stenosis (specificity 97 and 80%, respectively) ($p = 0.27$). In addition, 9 of 29 patients (31%) with aortic stenosis had inadequate studies compared with 9 of 52 patients (17%) with aortic regurgitation ($p = 0.17$). These differences were not statistically significant, possibly because of the small number of patients involved. The mean ages of the 2 groups were similar at 32 and 26 years, respectively ($p = 0.14$; not significant).

M-mode eccentricity index: Preoperative M-mode echocardiographic eccentricity indexes were determined in 54 of the 84 patients (64%). No eccentricity index was calculable in the remaining 30 patients because of multiple diastolic echoes in 20 and an inadequate echo of the aortic valve or aortic root in 10. A wide scatter of values was demonstrated (Fig. 4). With an eccentricity index of 1.3, the sensitivity and specificity for the bicuspid aortic valve were 55 and 71%, respectively.

Infective endocarditis: Of the 17 patients with history of infective endocarditis, 11 had tricuspid valves and 6 had bicuspid valves. Five of the 6 bicuspid valves were correctly diagnosed by 2-D echocardiography, and 1 was incorrectly diagnosed as tricuspid. Vegetations were diagnosed on 4 of the 6 bicuspid valves by 2-D echocardiography and later were confirmed at surgery in all cases. In the remaining 2 patients, no vegetations were seen on echocardiographic or surgical examination. Eight of the 11 tricuspid valves were correctly diagnosed by 2-D echocardiography, 2 were indeterminate, and one was mistakenly diagnosed as bicuspid. Vegetations were visualized on 2-D echocardiography on both indeterminate tricuspid valves and on 2 others, and all 4 were surgically confirmed. No false-positive diagnoses of vegetations occurred in either bicuspid or tricuspid valves.

Discussion

Normal aortic valves are tricuspid, with 3 near-equal-sized cusps. Various congenital abnormalities can occur, including tricuspid valves with significant unequal cusp size,[5] quadricuspid valves,[6] unicommissural valves,[7,8] and bicuspid valves.[2,3] Bicuspid valves may have 3 unequal aortic sinuses and a tall raphe along the conjoined cusp or only 2 aortic sinuses and a shallow raphe. These anatomic variations of bicuspid aortic valves can be visualized by 2-D echocardiographic techniques. Earlier claims of high sensitivity and specificity in the diagnosis of a bicuspid aortic valve with M-mode echocardiography have been challenged. Use of the maximal eccentricity index is limited because of various results depending on transducer angulation. Nanda et al[11] found that 10 patients with known bicuspid aortic valves had symmetric closure of cusps that depended on transducer angulation and also a change in cardiac cycle. Our eccentricity index data showed a wide range of results, with relatively low sensitivity and specificity for this technique in the diagnosis of bicuspid aortic valve.

A 2-D echocardiographic short-axis view of the aortic valve is a prerequisite for determination of the number of aortic cusps. Care should be taken that this tom

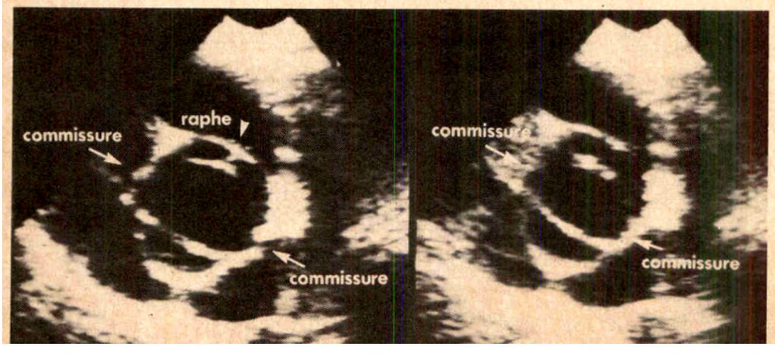

FIGURE 5. Parasternal short-axis views of bicuspid aortic valve in systole. **Left,** raphe is visible at approximately 1 o'clock. **Right,** scanning at a slightly more cephal

graphic section is perpendicular (aorta appearing circular) and not oblique. The tricuspid aortic valve has commissures at the 2, 6, and 10 o'clock positions, resulting in a letter Y configuration during diastole and an "inverted triangle" appearance in systole. In a bicuspid aortic valve, the commissures are usually at the 4 and 10 o'clock or 1 and 6 o'clock positions, and the cusps assume a fish-mouth appearance during systole. The results of the orientation of the commissures in our study were comparable to those of a previous pathologic study of 50 bicuspid valves.[12] The raphe was more or less perpendicular to the commissural orientation. Differentiation between a tricuspid valve with a true commissure and a bicuspid valve with a raphe is occasionally difficult, because the diastolic configuration can be similar. Study of the opening and closing pattern of the valve usually allows differentiation between the triangular-shaped tricuspid orifice and the characteristic fish-mouth–appearing bicuspid valve (Fig. 3). In addition, because most raphes are shallow and stop well below the cuspid line of closure, short-axis scanning above the valve produces "dropout" of the raphe and clearer visualization of the bicuspid nature of the valve (Fig. 5). Evaluation of cuspid motion is greatly facilitated by use of slow motion and stop frame.

When adequate images were available, we found that 2-D echocardiography was a sensitive and highly specific noninvasive method in the detection of bicuspid aortic valves. The specificity was especially remarkable, only 2 of 49 tricuspid valves being mistakenly diagnosed as bicuspid. Pathologic examination was not available for either of these valves. Determination of the number of aortic cusps was limited by either inadequate visualization of the cusps or dense valvular calcification, which prevented a diagnosis in 29 of the 115 patients (25%). This figure is comparable to that in previous studies of the feasibility of visualizing the aortic valve.[13] Adequate visualization of the valve was better in younger patients, because only 13% of patients aged ≤ years had indeterminate examinations.

The most useful application of this technique is in t evaluation of the asymptomatic patient in whom outflow systolic ejection murmur, a short aortic diasto murmur, or an ejection click (1 or more of these sign makes the clinician suspect bicuspid aortic valv Confident diagnosis of bicuspid aortic valve by 2 echocardiography in such a patient is clinically impo tant because it identifies a subset of patients who a at high risk for future complications.

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Classification of the Site of Ventricular Septal Defect by 2-Dimensional Echocardiography

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Sixty-three consecutive patients aged 2 months to 27 years with simple ventricular septal defect (VSD) or the syndrome of Fallot's tetralogy were prospectively investigated with 2-dimensional (2-D) echocardiography to assess the accuracy of the method in defining the anatomic site of the VSD. Twenty-two patients were referred for surgery without invasive investigation. The anatomy was confirmed in all patients at operation. Two-dimensional echocardiography was reliable in identifying subaortic, inlet, small, moderate, and large subtricuspid, large subpulmonary, and most large central and apical muscular VSDs. Mistakes were made initially in distinguishing doubly committed subarterial defects from subaortic VSD because of difficulty in imaging the right ventricular outflow in short axis at the aortic root level, small subpulmonary defects obscured by prolapsed aortic cusp tissue, and small apical or outlet muscular VSDs because of difficulty in distinguishing true "dropout" from trabeculations. Other VSDs particularly muscular, were sometimes overlooked after another large VSD had been identified. Thus, identification of the anatomic site of VSDs by 2-D echocardiography is a reliable method that can replace invasive investigation in assessing the uncomplicated VSD before operation. Ventricular septal defects are classified as muscular or subvalvular and subdivided according to the valve to which the defect is related.

Two-dimensional (2-D) echocardiography is a useful noninvasive method of recognizing ventricular septal defect (VSD).[1–4] Because the site of a VSD is as important as its size in determining the natural history of the patient,[5] both must be known for proper management. The clinical and hemodynamic effects on the cardiovascular system are a good indication of the size of the defect, depending in part on the influence of associated lesions. However, the anatomic site of the VSD cannot be determined by clinical examination but can be identified by angiography[6,7] and now by 2-D echocardiography.[1–4] In the hope of replacing invasive investigation and defining possible sources of error of interpretation, a prospective study was undertaken to examine the accuracy of the anatomic information provided by 2-D echocardiography in patients with VSD who had subsequent surgical treatment.

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Nomenclature of congenital heart disease, particularly VSD, has received much attention. The chosen taxonomy depends in part on the basic discipline of the investigator. Surgeons, anatomists, embryologists, pathologists, radiologists, and cardiologists see the same thing from different viewpoints.

An ideal classification must be simple, easily communicated, involve what is visible and not developmental postulants, and be useful for all disciplines. Thus is introduced another classification of VSD, intentionally pragmatic, simple, precise, and comprehensive. It is also applicable, without adaptation, to more complex anomalies in which VSD is one part of the anatomic disturbance.

Methods

Between November 1980 and February 1982, 63 consecutive patients aged 2 months to 27 years with VSD were prospectively examined by 2-D echocardiography in the National Heart Hospital. The age range of these patients was as follows: <1 year, 11 patients; 1 to 5 years, 14; 6 to 10 years, 12; 11 to 15 years, 10; 16 to 20 years, 9; >20 years, 7 patients. Criteria for inclusion in this study were (1) atrioventricular (AV) concordance, ventriculoarterial concordance, and situs solitus (patients with AV defects [common AV canal and intermediate forms], double outflow right or left ventricle, and any

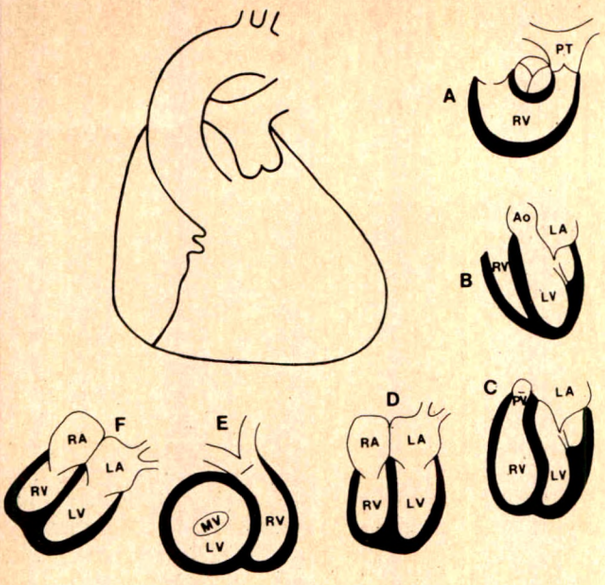


FIGURE 1. Diagram illustrating the bidimensional echocardiographic planes used in this study. *Parasternal:* **A,** short-axis great arteries (Fig. 6 and 8); **B,** long-axis left ventricle (Fig. 5, 9, and 10); **C,** long-axis right ventricular outflow tract (Fig. 11). *Apical:* **D,** 4-chamber (Fig. 3 and 4). *Subcostal:* **E,** long axis of the right ventricular outflow tract (Fig. 7); **F,** 4-chamber. Ao = aorta; LA = left atrium; LV = left ventricle; MV = mitral valve; PT = pulmonary trunk; PV = pulmonary valve; RA = right atrium; RV = right ventricle.

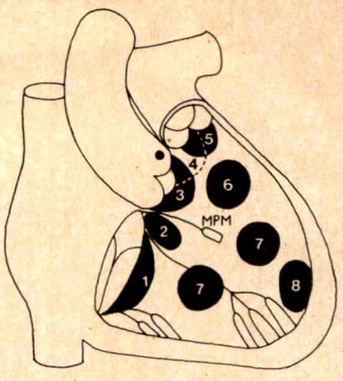


FIGURE 2. Anatomic diagram illustrating the position of the defects according to our classification. 1 to 5, subvalvular; 6 to 8, muscular. **1,** inlet; **2,** subtricuspid; **3,** subaortic; **4,** subarterial doubly committed; **5,** subpulmonary; **6,** outlet; **7,** central; **8,** apical. MPM = medial papillary muscle (muscle of Lancisi).

ticulous description at open-heart surgery; (3) technically satisfactory 2-D echocardiography with full visualization of the ventricular septum was mandatory and observed by each investigator. The site of the VSD was defined and recorded before operation.

Thirty-eight patients had either single or multiple VSD; 25 had Fallot's tetralogy with various degrees of obstruction of the right ventricular outflow tract. The VSD was complicated by Ebstein's anomaly in 1, aortic regurgitation in 6, coarctation of the aorta in 2, interrupted aortic arch with parachute mitral valve in 1, persistent ductus arteriosus in 2, and straddling tricuspid valve in 3.

Open-heart surgery was performed in all patients, 22 of whom had no preoperative invasive investigation.

Two-dimensional echocardiograms were taken initially with a phased-array electronically focused 3.5-MHz probe (Toshiba) and subsequently, in most, with a mechanical sector scanner inline 3-MHz probe (Advanced Technology Laboratories). Patients were studied in the supine or left lateral 30° decubitus position. The transducer was so placed as to show the ventricular septum in different planes using selected tomographic views of the heart, obtaining long- and short-axis parasternal views, apical 4-chamber views, and subcostal short-axis and 4-chamber views[8] (Fig. 1).

Two-dimensional echocardiograms were interpreted before angiography and surgery. All were reviewed after receiving detailed anatomic information from the surgeon.

Nomenclature of VSD

Ventricular septal defects occurred in 1 of 2 parts of the ventricular septum, either subvalvular or muscular. Subvalvular VSDs were directly related to AV or semilunar valves, or both, without any interposed muscle tissue between the hole and the valve cusps which formed a border or limiting boundary. Muscular defects were those bordered by muscle and not immediately related to AV or semilunar valves, or both.

Ventricular septal defects in the subvalvular group were subdivided according to the contiguous valve or valves (Fig. 2), as follows:

Inlet: This VSD lies beneath the septal leaflets of both AV valves and extends posteriorly beneath the tricuspid leaflet close to the crux or posterior ridge. Both AV valves are attached at a common level to the base of the atrial septum (central fibrous body). Associated straddling or overriding of the AV valves, or both, was frequent. This defect has been referred to elsewhere as AV canal type,[9] VSD in the posterior septum,[10] and perimembranous inlet.[4]

Subtricuspid: This common VSD is under the septal cusp of the tricuspid valve which frequently has chordal attachments to its borders and an abnormality or acquired deformity of the contiguous cusp. This defect does not extend as far posteriorly as inlet VSD, and the mitral valve is separated from the tricuspid valve by the AV septum so that the AV valves are not at the same level as in inlet defects. Subtricuspid VSDs have previously been termed inlet muscular,[11] VSD posterior to the medial papillary muscle,[12] infracristal, and perimembranous inlet defects.[4]

Subaortic: This type of VSD is usually large and immediately beneath the aortic valve cusps which form the cephalad border and which can be seen, particularly the right and noncoronary cusps, pouting through the defect when viewed from the right ventricle. The defect may extend posteriorly to the tricuspid anulus, may be associated with various degrees of malalignment of the ventricular septum, and is separated from the pulmonary valve and right outflow by infundibular septum. It is the VSD in classic Fallot's tetralogy. Previously, this subaortic VSD[5] was termed VSD anterior to the medial papillary muscle,[12] perimembranous (subaortic) outlet,[11] infracristal, or high.

Subpulmonary: This type of VSD is located in the outflow tract of the right ventricle. The superior border is formed by the pulmonary cusps and pulmonary anulus. It is separated from the aortic valve by a remnant

TABLE I Echocardiographic Identification of VSD and Surgical Correlation in 63 Patients

Type of VSD	Patients (n)	Surgery and Previous Angiography		2-D Echocardiography	
		+	0	Visualized	Position Identified
Inlet	8	4	4	8	8
Subtricuspid	7	5	2	5	4
Subaortic	30	16	14	30	30
Subpulmonary	2	2	. . .	1	1
Doubly committed subarterial	8	6	2	7	6
Apical	2	2	. . .	1	1
Central	3	3	. . .	3	3
Outlet	3	3	. . .	. . .	. . .
Total	63	41	22	55	53

2-D = 2-dimensional; VSD = ventricular septal defect.

part of the deficient infundibular ventricular septum. These defects are often small and associated with prolapse of the right coronary cusp in older patients, which is unusual in children <4 years of age. Large subpulmonary VSDs were uncommon in this group. Subpulmonary defects, small and large, have been called supracristal,[12–15] anterior infundibular,[16] infundibular septal, high, and perimembranous outlet/subpulmonary.[10]

Doubly committed subarterial: This type of VSD is also located in the outflow tract of the right ventricle immediately below the pulmonary valve but also extending beneath the aortic valve. There is fibrous continuity of the aortic and pulmonary anuli, and the infundibular septum is completely or partly absent. This defect may be isolated or coexist with pulmonary valvular stenosis presenting clinically as Fallot's tetralogy. Prolapse of both right and noncoronary cusps sometimes occurs. The doubly committed subarterial VSD lies either mainly beneath the aortic valve extending to beneath the pulmonary valve "ring," as in atypical Fallot's tetralogy, or more beneath the pulmonary "ring" and extending posteriorly to below part of the aortic valve. The latter type is often associated with pulmonary vascular disease and sometimes coarctation of the aorta. Hence, there is a need to understand the importance of these apparently minor differences in position as clearly there is a difference in blood flow during fetal life with different consequences in postnatal life. These defects have been named supracristal,[12,13,15] subpulmonary,[17] and complete infundibular septal,[16] and are separately distinguished from muscular and perimembranous as doubly committed subarterial defects.[10]

Muscular defects also were subdivided according to their position in the muscular ventricular septum (Fig. 2):

Apical: The VSD is situated near the apex of the heart caudal to the trabecular septomarginalis. Defects are single or multiple; when large, they resemble lattice work. Apical defects have been described as low[18] and, when multiple, as Swiss cheese.[16]

Central: This type of VSD occurs in the midportion apex and the plane of the AV valves. These defects are single or associated with subvalvular defects, small or large. This defect has been referred to as low, infracristal, and trabecular muscular VSD.[11]

Outlet: Outlet muscular VSD is found in the outflow tract of the right ventricle above or in a limb of the trabecular septomarginalis. The superior border of this defect extends up to or is located within the infundibular septum. This VSD is separated from the pulmonary valve by muscle of the infundibular ventricular septum. Such defects have been called high, anterior muscular,[16] and supracristal.[12,15]

Defects in the "posterior" [10] part of the septum were not recognized in this series.

Results

Ventricular septal defect was clearly identified by 2-D echocardiography in 55 patients (88%) (Table I). In 8 in whom it was not "seen" by 2-D echocardiography it was subsequently found to be subtricuspid in 2, small muscular outlet in 3, muscular apical in 1, subpulmonary in 1, and shallow, doubly committed subarterial in 1 in whom cusp tissue almost closed it. The position of the VSD was wrongly diagnosed in 2 patients, in 1 with a subtricuspid defect where it was thought to be subaortic because of false "dropout." In the other patient with clinical signs of Fallot's tetralogy, the VSD was defined as subaortic when it was doubly committed subarterial. This error occurred early in our experience and was not made in the last 30 patients.

The diameter of the VSD detected by 2-D echocardiography, as measured at surgery, ranged from 4 to 18 mm and that of the undetected VSD 2 to 6 mm. Echocardiography was reliable in detecting large VSDs.

Subvalvular Defects

Inlet: Eight patients aged 5 months to 8 years had this type of VSD; 3 of the 8 had a straddling tricuspid valve. All had surgical closure, without previous catheterization in 4, and clinical features suggested a large defect measuring 12 to 18 mm at operation.

Two-dimensional echocardiography: The defect was correctly sited in all and easily seen when the ventricular

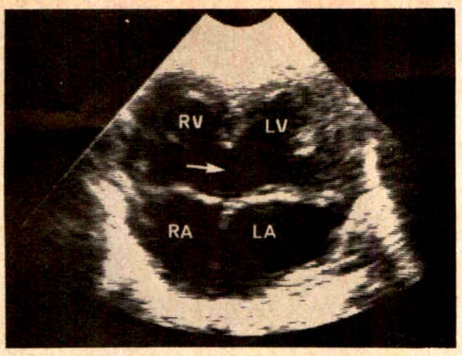


FIGURE 3. Apical 4-chamber view in an 8-year-old patient with inlet VSD. The dropout (**arrow**) appears beneath both septal leaflets. The AV valves are attached at the same level to the base of the interatrial septum. The atrioventricular septum is deficient. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

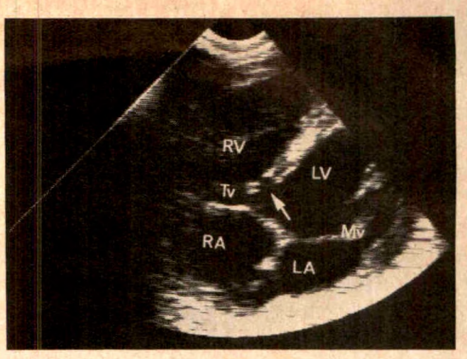


FIGURE 4. Apical 4-chamber view in an 18-month-old patient with subtricuspid defect. The VSD (**arrow**) lies beneath the septal cusp of the tricuspid valve. Both AV valves are attached at different levels of the interventricular septum, separated by the atrioventricular septum. Note also marked malalignment of the ventricular and atrial septa. LA = left atrium; LV = left ventricle; Mv = mitral valve; RA = right atrium; RV = right ventricle; Tv = tricuspid valve.

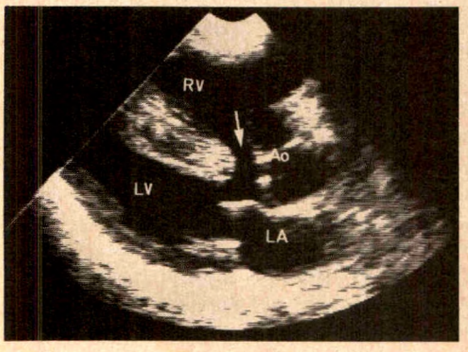


FIGURE 5. Parasternal long-axis view in a 16-year-old patient with Fallot's tetralogy and aortic regurgitation. The **arrow** shows the subaortic VSD between the aortic cusps and the crest of the malaligned interventricular septum. The aortic valve is thickened and there is no coaptation of the aortic cusps in diastole. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

position. The VSD appeared as an obvious large lack of ventricular septal tissue beneath both septal leaflets of the AV valves which were attached at the same level to the central fibrous body at the base of the atrial septum (Fig. 3). From apical and subcostal views, the tensor apparatus of the AV valves was carefully studied; abnormal insertion of the tricuspid valve into the left side of the ventricular septum was seen in 2 of the 3 patients in whom a straddling tricuspid valve was found at operation. In the parasternal long-axis view of the left ventricle the ventricular septum appeared to be intact in 6 of 8 patients with inlet VSD. In the other 2 with the largest defects, "dropout" was seen 0.5 cm beneath the aortic valve and subaortic extension was found at surgery. One patient had an additional large apical muscular VSD which was missed on 2-D echocardiography and at operation. It was confirmed at reoperation after catheterization.

To exclude a true common AV canal the atrial septum and the morphology of the AV valves were specifically studied.

Subtricuspid: This type of VSD was present in 7 patients aged 5 months to 25 years; coarctation of the aorta coexisted in 2 and Ebstein's anomaly in 1. Surgical closure of the VSD was performed without previous catheterization in 2. The size of the VSD at operation was 10 to 15 mm.

Two-dimensional echocardiography: This VSD was seen in 5 of 7 patients. In the 2 patients in whom a subtricuspid defect was overlooked, there was another large central muscular VSD. The position of the VSD was correctly identified in 4 of the 5 patients in whom the VSD was seen; in 1 the defect was erroneously considered to be subaortic. The VSD was best seen in apical and subcostal 4-chamber views in which the VSD appeared just beneath the septal cusp of the tricupid valve; the hole appeared to be sealed during diastole and open in systole (Fig. 4). The septal attachments of the AV valves were obviously separated by the line of AV septum. In the parasternal long-axis view of the left ventricle the VSD sometimes could be seen as "dropout" beneath the aortic valve in the subaortic area but separated from the anterior wall of the aorta by a bar of muscle <1 cm beneath the aortic valve. This part o subaortic septum was not seen in the 1 patient in whon the VSD was wrongly identified as being subaortic.

Subaortic: This type of VSD was present in 30 pa tients aged 6 months to 27 years, 20 of whom had Fal lot's tetralogy. The defect was complicated by paten ductus arteriosus in 2 and an interrupted aortic arc with parachute mitral valve in 1. Associated aorti regurgitation was found in 2, aged 16 and 27 years, wit Fallot's tetralogy. The position of the VSD was con firmed at surgery in all. Fourteen of the 30 patients wer referred for surgery without previous cardiac cathe terization. The size of the VSD ranged between 14 an 18 mm.

Two-dimensional echocardiography: The VSD wa always correctly identified. It was obvious in th parasternal long-axis view of the left ventricle as a lon discontinuity (hole) between the anterior wall of th aorta and the right aortic cusp and the crest of th ventricular septum (Fig. 5). No septal muscle or tissu was present between the VSD and the aortic cusps, an

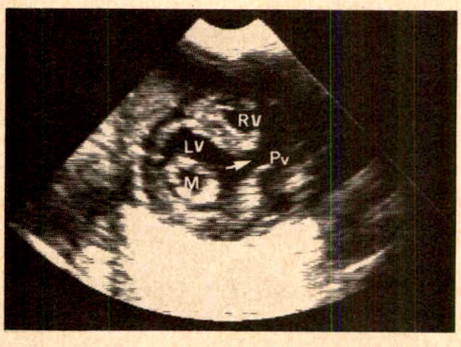
here was malalignment of the ventricular septum which n diastole was directed to the point of aortic valve closure. In the short-axis view of the aorta, the defect was seen beneath the right coronary cusp and that part of he noncoronary cusp extending usually to the tricuspid ring (Fig. 6). It was separated from the pulmonary valve by the solid muscle formed by the infundibular septum which in patients with Fallot's tetralogy was thickened rom hypertrophy with dense endocardial echoes. In the 2 patients with Fallot's tetralogy and aortic regurgitation the right coronary cusp was large, thickened, and prolapsed into the defect. In 1 of them there was fluttering of the crest of the ventricular septum from the egurgitant jet, and the aortic cusps did not coapt in liastole (Fig. 5).

Subpulmonary: Two patients aged 2 and 12 years had subpulmonary defects proved by surgery. The defect was small (8 mm) in 1 with aortic regurgitation from prolapse of the right coronary cusp into the defect. In he other, the VSD was 12 mm in diameter.

Two-dimensional echocardiography: The position f the VSD was correctly identified in 1 of the 2 patients. n a 12-year-old boy with aortic regurgitation in whom he VSD was not seen, cusp tissue was present in the mall defect and was visible on angiography, and a pansystolic murmur suggested its presence. In this patient t had been difficult to assess the right ventricular outlow tract from the subcostal position, and thus the lefect was not seen. The subpulmonary VSD in the patient in whom it was correctly sited appeared as dropout" under the pulmonary valve without interposed muscle when the right ventricular outflow tract vas scanned from the subcostal position (Fig. 7).

Doubly committed subarterial: This defect was present in 8 patients aged 4 months to 27 years. Five atients aged 14 to 27 years had the clinical features of allot's tetralogy, with associated aortic regurgitation rom prolapse of the right coronary cusp in 3. All had peration, 2 without previous cardiac catheterization. he size of the defect was 12 to 18 mm.

Two-dimensional echocardiography: Seven of 8 oubly committed subarterial defects were identified y 2-D echocardiography. In 1 with Fallot's tetralogy,



IGURE 7. Subcostal scanning of the right ventricular outflow tract in 2-year-old patient with subpulmonary VSD. The **arrow** shows the efect. There is no septal muscle between the hole and the pulmonary alve. LV = left ventricle; MV = mitral valve; PV = pulmonary valve; V = right ventricle.

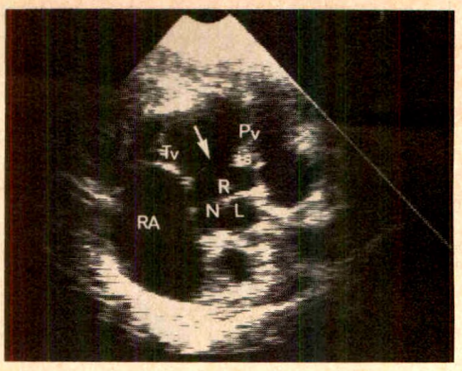


FIGURE 6. Parasternal short-axis view of the aorta in a 12-year-old patient with isolated subaortic VSD. The defect (**arrow**) lies beneath the right coronary cusp extending to the tricuspid ring. The infundibular septum separates the VSD from the pulmonary valve (Pv). IS = infundibular septum; L = left coronary cusp; N = noncoronary cusp; R = right coronary cusp; RA = right atrium; Tv = tricuspid valve.

the VSD was wrongly thought to be confined to the subaortic area as in classic tetralogy of Fallot. In the parasternal long-axis view of the left ventricle the defect appeared to be only subaortic with the superior edge formed by the aortic cusps. In the short-axis view at aortic root level the VSD was beneath the right coronary cusp and that part of the left coronary cusp extending up below the pulmonary valve (Fig. 8). No infundibular septum was detected and the defect was clearly separated from the tricuspid valve ring.

Muscular Defects

Apical: A large VSD at the apex occurred in 2 patients aged 2 months and 4 years. All had cardiac catheterization and angiography before operation, with the defect measuring 12 to 13 mm.

Two-dimensional echocardiography: Apical defects were identified in 1 of the 2 patients. One with a large single apical VSD had large areas of "dropout" at the

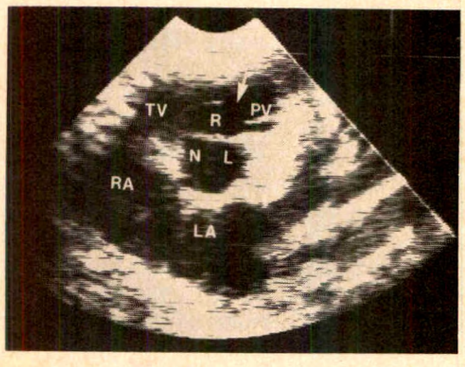


FIGURE 8. Parasternal short-axis view of the aorta in a 27-year-old patient with Fallot's tetralogy and doubly committed subarterial VSD. The defect (**arrow**) lies beneath the right coronary cusp extending up below the pulmonary valve. The infundibular septum is absent. The VSD does not reach the tricuspid ring. L = left coronary cusp; LA = left atrium; N = noncoronary cusp; PV = pulmonary valve; R = right coronary cusp; RA = right atrium; Tv = tricuspid valve.

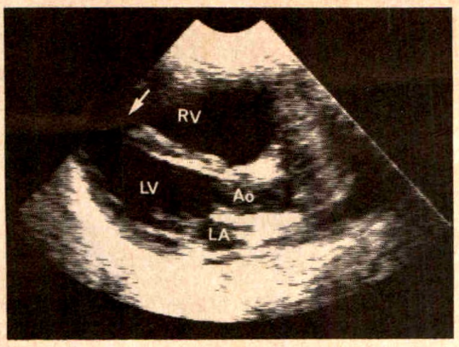


FIGURE 9. Parasternal long-axis view of the left ventricle in a 4-year-old patient with an apical muscular VSD. The dropout (**arrow**) appears near the junction of the interventricular septum with the free wall of the left ventricle. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

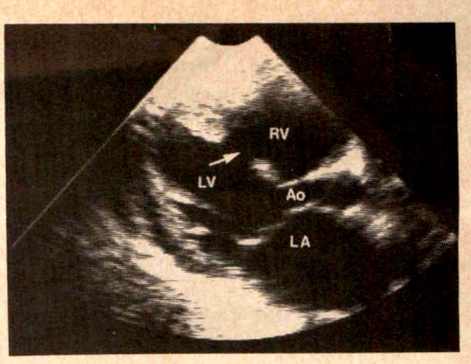


FIGURE 10. Parasternal long-axis view of the left ventricle in a 4-year-old patient with a central muscular VSD. The **arrow** shows the position of the defect which lies almost at the same distance between the apex and the aortic root. No valves are related to the defect. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

junction of the ventricular septum with the free wall of the left ventricle in 4-chamber and long-axis views of the left ventricle (Fig. 9). Scanning the left ventricle in short axis at the level of the papillary muscles, the ventricular septum appeared to be intact. Nevertheless, from this position and by tilting the transducer laterally to profile the apex, a defect was easily seen. The other patient with multiple small apical defects (Swiss cheese septum), no VSD was seen in any projection, but small defects between the trabeculae were found at operation.

Central: This muscular VSD occurred in 3 patients aged 2 to 4 years. All were catheterized before surgery. The size of the defects was 10 to 15 mm. In 2 patients there was an additional subtricuspid defect of 7 and 8 mm.

Two-dimensional echocardiography: The central muscular VSD was identified in all, but the associated subtricuspid defect in 2 was not seen, as just described. In parasternal long-axis view of the left ventricle the defect appeared as a lack of fusion of the ventricular septum, its center almost at the same distance from the apex and the aortic root (Fig. 10). In both apical and subcostal 4-chamber views the hole appeared equidistant from the apex, and the plane of the AV valves was adjacent to the trabecular septum marginalis.

Outlet: Three patients aged 14 to 19 years had a single outlet muscular defect 10 to 12 mm in diameter. All were catheterized before surgical closure.

Two-dimensional echocardiography: The VSD was not correctly recognized by 2-D echocardiography in any. The patients were well-built adolescents in whom it was difficult to profile the ventricular septum from the subcostal position, and no "dropout" in the ventricular septum was seen from any view scanned from precordial and apical areas. In 2 of the 3 patients the echocardiogram was repeated after operation in order to see the patch; this appeared only when imaging the long axis of the left ventricle and scanning anteriorly with 30° clockwise rotation of the transducer to see the right ventricular outflow tract (Fig. 11). The patch was not seen beneath the pulmonary valve in standard short-axis views or from the base of the heart.

Discussion

The anatomy of the ventricular septum has been precisely described, but confusion exists on the meaning and limits of various terms particularly when definitions involving embryologic postulants are used. Such commonly used terms as crista and infundibular septum mean different things to different workers.[19] Therefore, it is not surprising that the nomenclature of VSDs has been debated, confused, defined didactically, and redefined and has not resulted in a satisfactory simple classification acceptable to all the different disciplines involved in the management of patients or the heart with this common anomaly. Before VSD can be discussed, a useful terminology which can be communicated with ease and clarity is required. The now popular term *perimembranous*, although theoretically accurate and meaningful to some, includes several types of VSD[11] with very different natural histories, making inclusion under 1 heading unattractive to clinicians. In living patients, the exact site and limits of the membranous portion of the ventricular septum between the inlet and trabecular portion of the ventricular septum are diffi-

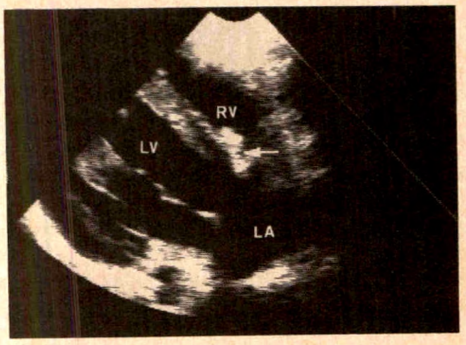


FIGURE 11. Postoperative echocardiogram in a 14-year-old patient who had an outlet muscular VSD. Parasternal long-axis view of the left ventricle with 30° clockwise rotation and scanning anteriorly to profile the right ventricular outflow tract. The **arrow** shows the position of the patch. The pulmonary valve does not appear in this plane. LA = left atrium; LV = left ventricle; RV = right ventricle.

cult to define because both appear trabeculated on echocardiography. Thus, imagination may be needed to define what surrounds something that may not be seen, particularly in hearts with more complex malformations. Furthermore, to distinguish among the various types of perimembranous VSDs, which is necessary, further wordy subdivision is needed. Therefore, it is preferable to describe holes in the ventricular septum in relation to structures, constantly present and universally recognized, that is, the aortic, pulmonary, and AV valves which can be sited without difficulty on angiography, 2-D echocardiography, anatomic inspection, and open-heart surgery. It is simple to name the VSD in relation to the valve directly beneath which it lies. When the VSD is separated from the valves by a bar of tissue, it lies in a part of the muscular septum that is divisible into regions in which defects may occur at the apex, center, or outflow. When the VSD is not confined to 1 area, a simple term *extending* can be added to describe it.

This classification is easy to use and readily applicable in more complex lesions associated with VSD, such as corrected transposition, double outflow, corrected malposition, and transposition of the great arteries.

In the current study, 2-D echocardiography was completely reliable in the diagnosis of subaortic and inlet VSD. Initially, occasional mistakes were made in distinguishing doubly committed subarterial VSD from subaortic VSD. Errors decreased after special care was taken in observing the short-axis view of the right ventricular outflow tract at the aortic root level to see the extent of the VS relation to the aortic cusps.[20] Other small subpulmonary and outlet muscular VSDs were also difficult to recognize in adolescents and adults. This part of the ventricular septum is well profiled from the subcostal position in infants and small children, but the view has limited application in older, larger patients. No difficulty was found in identifying these defects in infants and young children, unless there was associated prolapse of the right coronary cusp into the defect, and then the "dropout" of the VSD could be masked by the prolapsing cusp tissue into the defect.

The most significant errors were made in recognizing a second apical or central muscular VSD when 1 large VSD had already been found elsewhere. We suspect this might have been related to careless observation and complacency in finding 1 adequate explanation for the physical signs. This error is serious as the improperly briefed surgeon may overlook another muscular defect having already closed 1 in another part of the ventricular septum. Now, the muscular septum is more carefully scrutinized even when 1 VSD has been clearly located elsewhere. Recognizing multiple muscular (apical) small VSD was difficult because of the problem of distinguishing true holes from intertrabecular spaces.

This series by choice is concerned with moderate and large VSD in which it was possible to obtain surgical confirmation. However, the technique is equally applicable to small VSDs, particularly in the subtricuspid area in which they can be seen frequently surrounded by bright echoes due to fibrosis or attachment of tricuspid tissue, or both. Therefore, serial 2-D echocardiography is useful in identifying and following up those VSDs that will or are spontaneously closing. We now believe that 2-D echocardiography provides a reliable method for confirming the diagnosis and anatomic site of a VSD before surgery.

During the period of this study, many presurgical patients were investigated echocardiographically and sent for operation without previous catheterization. The wrong diagnosis of VSD was not made.

The present policy is not to carry out invasive investigation before surgery for uncomplicated VSD provided information is not required about pulmonary vascular resistance, the clinical features match the echocardiographic findings, and the anatomy of the right and left ventricular outflow tract is known. There is a risk of overlooking small or moderate muscular VSDs by not performing left ventricular angiography.

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Results After Repair of Coarctation of the Aorta Beyond Infancy: A 10 to 28 Year Follow-Up With Particular Reference to Late Systemic Hypertension

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The late outcome in 160 patients aged 1 to 54 years who had surgical repair of coarctation of the aorta was examined 10 to 28 years postoperatively. Twenty years postoperatively the probability of survival of patients discharged from the hospital aged 1 to 19 years at operation was a little less than that of the general population (95% versus 97%). The discrepancy between patients and the general population was more marked in those aged 20 to 39 years and was grossly different when surgical repair was undertaken beyond age 40. There were 19 late deaths (12%), 79% due to cardiovascular disease. Thirteen patients had a poor result because of recoarctation (11 patients) or the development of complications at the site of repair (2 patients).

Most patients were hypertensive before operation. The frequency of hypertension decreased markedly in the first few postoperative years. Blood pressure was normal in most patients 5 to 10 years after operation, but when followed up for longer periods the proportion of patients with hypertension increased. Hypertension was more common in patients operated on after 20 years of age than in those aged 5 to 19 years at operation ($p = 0.007$). The likelihood of being alive without complications and with a normal blood pressure was 69% at 10 years, 55% at 15 years, and 20% at 25 years postoperatively.

Despite the fact that surgical repair of coarctation of the aorta (C of A) was first undertaken in 1944,[1] little information is available on the long-term results of this treatment.[2–5] This report describes the outcome in 160 patients followed up ≥10 years postoperatively, with particular emphasis on the frequency of elevated systemic blood pressure (BP).

Methods

Of 160 patients aged 1 to 54 years operated on for C of A from May 1949 until December 1968, all but 1 of the late survivors were traced from 1979 to 1980, although 4 patients known to be alive were not available for review. Of the 155 patients, 54% were examined by us, 21% by cardiologists elsewhere, and 22% by other physicians. At the time of review their ages ranged from 13 to 72 years. The minimum follow-up in survivors was 10 years and the average, 17.5 years. Duration of follow-up was 20 to 24 years in 38 patients and 25 to 28 years in 8.

Repair of C of A was judged clinically to be *good* if the femoral pulses were normal on palpation or the systolic BP in the legs was the same as or greater than that in the arms, or both; *satisfactory* if there was only minor impairment of the femoral pulses or the BP in the legs was ≤20 mm Hg below that in the arm; and *poor* if there was marked reduction or delay of the femoral pulses, the BP in the legs was more than 20 mm Hg below that in the arm, or there were complications at the site of repair.

Cardiac catheterization studies were undertaken in 47 patients 1 to 20 years after operation (median 5 years), but few had adequate aortograms for review, and in most patients the study was performed >10 years before the present review.

Blood pressure was considered elevated if the systolic pressure was ≥160 mm Hg or the diastolic pressure was ≥95 mm Hg, or if, in patients <19 years of age, pressures were beyond the 95th percentile.[6] Patients receiving antihypertensive therapy also were considered hypertensive.

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TABLE I Age at Operation and Outcome

Age (yr) at Operation	Cases		Hospital Deaths*	Late Deaths	Alive		Residual/ Recoarctation	
	n	%	(n)	(n)	n	%	n	%
1–9	40	25	1	2	36	90†	6	15‡
10–19	62	39	2	2	58	94	3	5
20–29	26	16	. . .	4	22	85	2	8
30–39	16	10	. . .	3	13	81	. . .	. . .
40–49	11	7	. . .	4	7	64	. . .	. . .
50+	5	3	. . .	4	1	20	. . .	. . .
Total	160		3 (2%)	19 (12%)	137	86	11	7

* Thirty-day mortality.
† One patient not traced.
‡ None in patients aged <5 years.

TABLE II Preoperative Hypertension

Age (yr)	Cases (n)	Systolic and Diastolic Hypertension	Systolic Hypertension	Diastolic Hypertension	Normal Blood Pressure
1–9	40*	29	8	0	2
10–19	62	31	20	4	7
20–29	26	18	6	0	2
30–39	16	13	3	0	0
40–49	11	5	6	0	0
50 +	5	3	2	0	0
Total	160	99 (62%)	45 (28%)	4 (3%)	11 (7%)

* One patient included in this column did not have blood pressure measurement.

Preoperative and serial postoperative casual BP records were available. Those recorded at hospital discharge (usually 7 to 10 days after operation), 1 to 2, 5 (±1), 10 (±1), 15 (±1), and 20 (±1) years postoperatively were selected for analysis. In a few cases BP measurements were not available 20 years after operation but were available a few years later, and this measurement was then used in Figure 2. Because measurements were not available for all time intervals in each patient, certain assumptions were made. If the BP was known and fell into the same category 5 and 15 years postoperatively, it was assumed to be in this category 10 years postoperatively. It could not be assumed that patients who were hypertensive 1 to 2 years and 10 to 15 years postoperatively were necessarily hypertensive 5 years after operation, so that such patients were categorized as having no data at that time.

TABLE III Associated Lesions

Lesion	n*	%
Aortic incompetence	27 (5)	17
Aortic stenosis	7 (4)	4
Mitral stenosis (congenital)	1 (1)	0.6
Mitral incompetence	4	2
Patent ductus arteriosus	26 (26)	16
Large 2		
Moderate 2		
Small 22		
Ventricular septal defect	6 (1)	4
Large 3 (1)		
Small 3		
Atrial septal defect	1 (1)	0.6
Infundibular pulmonary stenosis	1	0.6
Multiple arterial stenoses	1	0.6
Aberrant right subclavian artery†	3	2
Stenosis at origin of left subclavian artery†	7	4
No associated lesion	98	61
Patent ductus arteriosus only	18	11
Total patients	160	100

* Figures in parentheses indicate operations for correction of the associated lesions.
† Not classified as associated lesion.
As more than 1 defect was encountered in some patients, the figures are not cumulative.

Graded exercise testing was undertaken in 24 patients (21 with resection and end-to-end anastomosis and 3 with aortoplasties). None was receiving antihypertensive medication or had a poor result from repair. The method used was that of Bruce et al[7] modified to exclude the first stage, exercise commencing with a treadmill gradient of 12% and a speed of 4 kph and continuing until maximum voluntary exercise capacity was reached. Blood pressure was measured in the right arm during exercise using a Bonn sphygmomanometer which incorporated a cuff automatically inflated to suprasystolic pressure and had a maximal reading of 300 mm Hg. On slow deflation the systolic and diastolic BP was recognized by recording the onset and cessation of sound with a microphone. The apparatus was checked regularly for accuracy using a standard mercury sphygmomanometer and remained stable. BP and heart rate were measured each minute during exercise and immediately afterwards (within 30 to 60 seconds of cessation of exercise) with the patient still standing on the treadmill.

Actuarial curves were constructed to illustrate late results.[8] Comparisons between curves were made.[9] Cumulative actuarial curves were constructed after the method of Grunkemeier et al.[10] Comparisons between groups were made using the 2-tailed unpaired t test. Differences were considered significant at $p < 0.05$.

Clinical profile of patients: Of the 160 patients, 108 (67%) were male and 52 female. Only 40 (25%) were <10 years and only 8 of these <5 years of age at operation (Table I). Hypertension was common (Table II). Thirteen of the 45 patients

TABLE IV Type of Repair

Type of Operation	Cases (n)	Poor Results (n)	Site of Aneurysms Preoperatively			
			AoI	AoPC	IC	Other
Resection + end-to-end anastomosis	120	4	3	1	3	1 (RSC)
Resection + end-to-end anastomosis + Dacron patch graft	4	...	...	...	...	...
Tube graft (end-to-end)	13	5*	...	3	1	...
Dacron patch graft (onlay)	13	2	...	...	...	...
LSC to descending aorta anastomosis†	4	2	...	...	...	...
Aortoplasty‡	6	...	...	...	...	...
Total	160	13	3	4	4	1

* Two of these patients had a poor result because of a postoperative aneurysm.
† The left common carotid artery was used in 1 patient.
‡ Vertical incision with transverse closure in 4, excision of part of the circumference in 1 and excision of the diaphragm only in 1.
AoI = aortic isthmus; AoPC = aorta beyond coarctation; IC = intercostals; LSC = left subclavian artery; RSC = right subclavian artery.

with systolic hypertension had aortic regurgitation (AR), but in only 3 was this thought to be hemodynamically important. Four patients had a previous subarachnoid hemorrhage. Myocardial infarction had occurred in 1 patient and angina pectoris in another, and 4 had bacterial endocarditis before operation. Eight patients had previously been treated for heart failure.

Associated lesions: Associated lesions present either before or after C of A repair are listed in Table III. Aortic regurgitation was found in 27 of the 36 patients with valve lesions. Fifteen had mild AR at the time of the C of A repair. It remained mild in 13 patients aged 20 to 62 years (average 40 years) when last seen and had become moderate in 1 and severe in another who had late postoperative endocarditis and subsequent aortic valve replacement. Five patients had important AR at the time of C of A repair and aortic valve replacement was later undertaken in the 4 hospital survivors. In 7, AR (mild in 6, moderate in 1) was first noted during the postoperative follow-up. Aortic stenosis of at least moderate severity was noted in 7 patients; 4 have had aortic valve surgery. In 1 early case the patient died with severe stenosis without operative treatment. Congenital mitral stenosis was seen in 1 adult who underwent valvotomy. Mitral regurgitation was noted in 4 patients, 2 of whom also had AR, but in none was it severe enough to warrant valve surgery.

Type of operation: The most commonly used technique was resection of the C of A and end-to-end anastomosis (Table IV). The ductus, when patent, was divided. Aneurysms were present in 12 patients (Table IV) and were either excised along with the C of A (except for 1 involving the right subclavian artery), or when they involved the upper intercostals, the vessels were divided and oversewn.

Postoperative complications: Important postoperative hemorrhage occurred in 10 patients, and reoperation was undertaken in 7. Mesenteric arteritis was diagnosed in 9 patients (6 male, 3 female). Two underwent laparotomy but neither required bowel resection, and both recovered. Another 12 patients (10 male, 2 female) complained of postoperative abdominal pain.

Paraplegia occurred in 2 patients. One had an associated saccular aneurysm which was resected along with the area of mild C of A and replaced by a Dacron® tube graft. The other had large patent ductus arteriosus opening directly into the aorta distal to the C of A which was resected, the aorta being intermittently cross-clamped for 30 minutes after the ductus had been divided. Both patients had minimal collateral development.

Chylothorax occurred in 4 patients and temporary hoarseness was noted in 2 (in 1 of whom Horner's syndrome also developed). There were single instances of damage to the left phrenic nerve, septicemia, cerebral symptoms, jaundice, and pleural effusion.

Results of operative treatment: The late outcome in 159 of the 160 patients is known (Table I). There were 3 hospital deaths (2%). Two occurred in 1949 (1 in association with important AR), and only 1 hospital death (associated with ven-

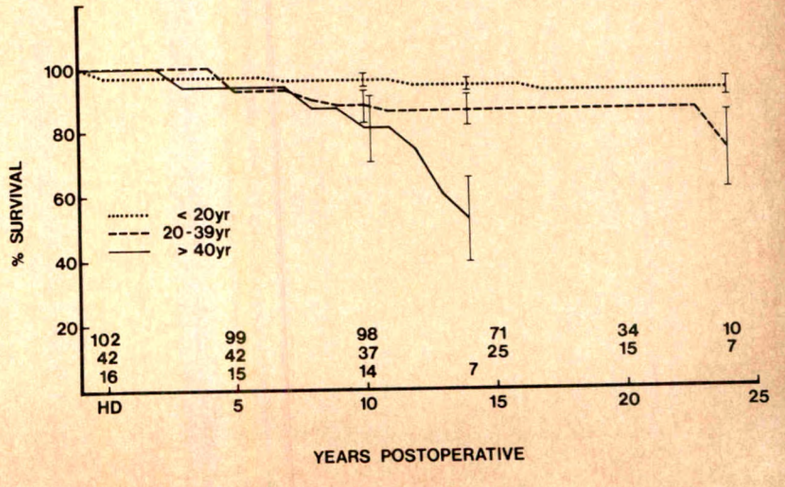

FIGURE 1. Actuarial curves relating chance of long-term survival to age at operation. Hospital deaths are included. The figures below the curves refer to the numbers of patients at risk at the different time periods. The bars on the curves represent the standard error. The same format is used in subsequent figures.

TABLE V % Probability of Survival After Repair of Coarctation in Hospital Survivors Compared With the General Male Population

Age (yr) at Operation	Percent Chance of Survival: Years of Follow-up		
	+10	+15	+20
1–9	97 (99)*	95 (99)	95 (98)
10–19	100 (98)	98 (98)	95 (97)
20–29	92 (99)	88 (97)	88 (96)
30–39	81 (97)	81 (94)	81 (90)
40–55	81 (90)	52† (81)	. . .

* Figures in parentheses refer to general male population.
† Patients actually only followed up to 14 years postoperatively.

tricular septal defect, patent ductus arteriosus, and an elevated pulmonary vascular rersistance) in the last 157 patients (0.6%).

There have been 19 late deaths 2 to 23 years after operation. Autopsy was performed in 14. Fifteen deaths were due to cardiovascular disease. In 3 death was related to C of A; in 1 a dissecting aneurysm proximal to a tube graft developed 16 years after operation, 1 patient died 23 years after operation with detachment of a Dacron patch graft which had been used to revise the original repair 8 years previously, and the third died 11 years postoperatively from hemoptysis which appeared to arise from intercostal arteries. Six late deaths were due to coronary heart disease, 4 to aortic valve disease, 1 to associated congenital heart disease and pulmonary vascular obstruction, and another to poor left ventricular function present before operation. Two patients died after motor vehicle accidents, and the cause of death in 2 patients is unknown. Age at operation was significantly greater ($p < 0.001$) in patients who died late (33 ± 16 years) than in those who were long-term survivors (18 ± 11 years). The average age at death was 41 years.

Actuarial survival was 81 ± 6% (standard error) 24 years postoperatively. There was no significant difference in late survival between individual decades up to the fourth. In patients operated on at 1 to 19 years of age, 96, 94, and 92% were alive 10, 15, and 24, years postoperatively (Fig. 1), and of those aged 20 to 39 years, 88, 86, and 73% ($p = 0.09$). In patients >40 years at operation, the chance of survival was 81% 10 years after operation and only 52% 14 years postoperatively ($p = 0.007$ when compared with those aged 20 to 39).

The probability of survival in those discharged from the hospital was compared with that of a general male population[11] (Table V). The probability of survival 20 years postoperatively in patients aged 1 to 19 years at operation was a little less than that of the general population. The discrepancy between patients and the general population was more marked in those aged 20 to 39 years at operation and grossly different when surgical repair was undertaken after the age of 40 years.

Results of repair of C of A were known in 149 patients. Eighty-nine (57%) were judged clinically to have a good result and 47 (30%) a satisfactory result. Thirteen (8%) had a poor result because of either the development of an aneurysm (2 patients) or residual or recoarctation (11 patients). The latter was noted in 3.3% of patients after resection and end-to-end anastomosis (Table IV) and in 17.5% of those with other types of repair, reflecting more complex anatomy unsuited to simple resection. Revision of the repair was undertaken in 7 of the 11 patients without any hospital mortality and with relief of the obstruction in all.

Seventeen patients without recoarctation who were followed up beyond the 20th postoperative year had catheterization studies 1 to 20 (median 6) years after operation, all being over 16 years of age at the time. Only 1 of the 6 patients without a gradient across the anastomosis and 6 of the 11 patients with a small gradient were normotensive when last reviewed. Two patients had aortograms which showed that the anastomotic diameter was at least as wide as the lower thoracic aorta. One patient was normotensive, the other hypertensive. In 3 patients the anastomotic diameter was 72 to 82% of the lower aorta. Two of these patients were normotensive and 1 hypertensive.

Incidence of systemic hypertension: The frequency of hypertension before and after operation in 138 hospital survivors who were >5 years of age at operation and who did not have evidence of residual or recoarctation is summarized in Figure 2. There was no significant difference in the incidence of hypertension when those who had a good result after repair were compared with those who had a satisfactory result ($p = 0.18$).

Most patients were hypertensive before operation. Some became normotensive before hospital discharge whereas others became normotensive within 1 to 2 years. A few patients with elevated BP at this time were subsequently normotensive. A normal BP was present in most patients 5 to 10 years postoperatively, but with longer periods of follow-up the proportion with hypertension increased. The pattern was similar in all age groups.

The same data have been analyzed actuarially (Fig. 3). When each age group is compared with the next highest age

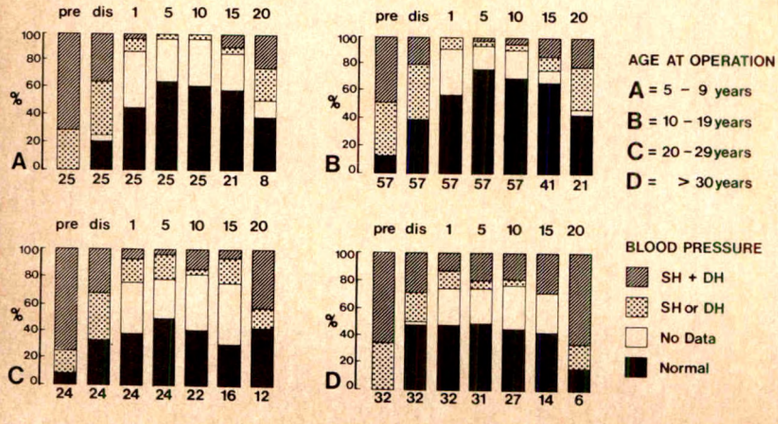

FIGURE 2. Blood pressures in 138 hospital survivors >5 years of age who did not have recoarctation are grouped according to age at operation. The numbers above the bars refer to years after operation. The numbers below the bars refer to the number of patients at risk in each time period. DH = diastolic hypertension; dis = hospital discharge; pre = preoperative; SH = systolic hypertension.

group, there is no significant difference between each pair of curves. However, hypertension was more common in patients operated on after 20 years of age than in those aged 5 to 19 years ($p = 0.007$). Both the 5 to 9 year age group and those aged 10 to 19 years at operation have a significantly lower incidence of hypertension than do patients >30 years of age at operation ($p = 0.02$ and 0.001).

The effect of important AR on the development of systolic hypertension was examined. In only 1 patient in whom moderate AR developed 19 years postoperatively was this a likely contributory factor, as other patients with severe AR were normotensive according to the definition used, or the timing of aortic valve replacement was such that there was no effect on BP at the time of analysis.

Forty-five patients aged 5 to 39 years at the time of repair were followed up beyond the twentieth postoperative year. Eight of the 13 who were normotensive at hospital discharge were normotensive when last seen. In contrast, only 7 of the 32 patients who were hypertensive at hospital discharge had a normal BP when last reviewed, that is, patients who were normotensive at discharge are more likely to have a normal BP very late postoperatively ($p = 0.03$).

Of the 125 late survivors with a good or satisfactory result from repair, 121 were <60 years of age when last reviewed. Of the 84 who were <40 years of age, 36% at review were hypertensive as were 78% of the 37 patients aged 49 to 59 years. These figures are contrasted with the prevalence of hypertension in patients in these age groups in the general population (using the same criteria as used in this study), where it was 4 and 17%, respectively.[12] Although 47% of 129 late survivors without recoarctation were hypertensive when last reviewed, only 28% of the 60 hypertensive patients had a BP ≥180 mm Hg systolic or ≥110 mm Hg diastolic.

Exercise testing: Results of graded exercise testing 11 to 25 years after operation in 24 patients who attained a heart rate of at least 85% of maximum for age[13] after 6 to 15 minutes (average 11) were examined. Age at operation was 7 to 40 years (average 17), and at testing 21 to 59 years (average 34). Eight patients were normotensive, 16 were hypertensive but on no treatment, and none had a poor result. A decrease in BP occurred within 30 to 60 seconds of stopping exercise in many patients (Fig. 4). No major differences were found when maximum systolic pressure with exercise was examined in relation to age at operation, age at testing, a good or satisfactory result of the C of A repair, or the achievement of maximal or submaximal heart rate with exercise. Average systolic BP with exercise was not significantly higher in patients who were hypertensive at rest than in those who were normotensive (285 ± 23 versus 266 ± 26 mm Hg; $p = 0.08$).

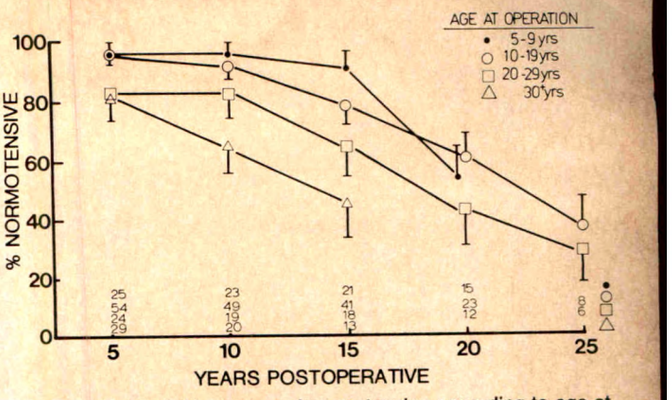

FIGURE 3. Actuarial incidence of normotension according to age at operation and the time of postoperative follow-up.

Two patients aged 9 and 23 years at operation were shown 2 to 7 years postoperatively to have no gradient across the anastomotic site which was at least as wide as the lower thoracic aorta on aortography. Both were hypertensive on review at 31 and 48 years, but had relatively low systolic pressures with exercise (160 → 250 mm Hg and 170 → 235 mm Hg).

Other postoperative morbidity in late survivors: At the time of review, 138 patients were alive, and recent medical assessment was available in all but 4. Exercise tolerance was normal in 114 of the 134 assessed patients (85%), mildly impaired in 19 (14%), and significantly reduced in 1.

Myocardial infarction occurred in 1 patient who experienced angina before operation, and an additional 5 patients developed angina. Cerebrovascular disease was noted late postoperatively in 4 patients. One hypertensive patient had a subarachnoid hemorrhage associated with a Berry aneurysm 17 years postoperatively, and in another a Berry aneurysm was found 8 years after operation when cerebral arteriography was performed because of episodic vertigo and headache. One

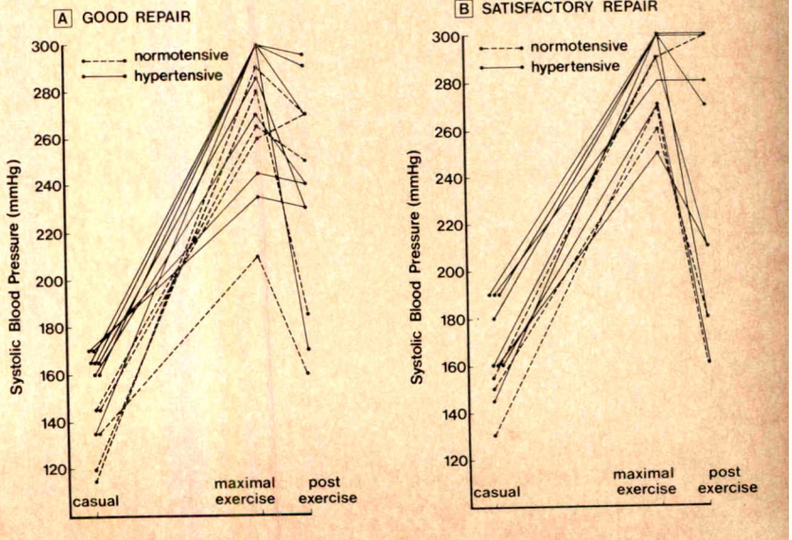

FIGURE 4. Response of arm systolic blood pressure to exercise. Blood pressure within a minute of stopping exercise is also shown. **Left,** patients with good repair; **right,** patients with satisfactory repair.

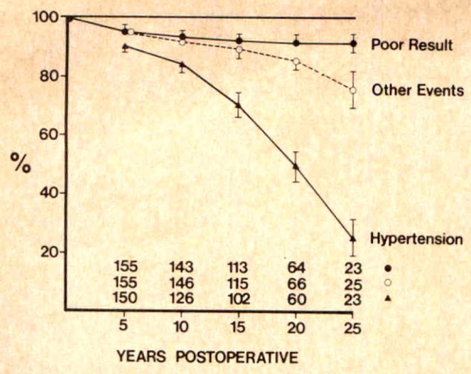

FIGURE 5. Individual actuarial curves showing the percent chance of freedom from postoperative complications.

patient with cerebral symptoms had left vertebral artery stenosis and 1 patient with a Braunwald-Cutter aortic prosthesis had a cerebral embolus. The 4 patients who had a subarachnoid hemorrhage preoperatively had no recognized recurrence 12 to 19 years after operation. Neurosurgical treatment had been undertaken in 1 of the 2 in whom Berry aneurysms were demonstrated. Evidence of degenerative hip disease[2] was not specifically sought, but overt problems were noted in 2 patients.

Summary of late results: The long-term course of hospital survivors is summarized in individual actuarial curves (Fig. 5). By 25 years postoperatively, 8% had a poor result. Important associated disorders, usually valve lesions requiring surgical treatment or symptomatic coronary or cerebrovascular disease, have been grouped together, are shown as "events," and were seen in 25%. Hypertension was noted in 75%.

The late postoperative course is also summarized in cumulative actuarial curves (Fig. 6), with complications arranged in an hierarchical manner. When more than 1 complication occurred in an individual patient, it was placed in the uppermost category.

The incidence of late deaths increased with increasing duration of follow-up as did the proportion of patients with events and hypertension. The percentage of patients who were alive without complications and with a normal BP was 69% at 10 years, 55% at 15 years, and 20% at 25 years postoperatively.

Discussion

We elected to confine this analysis to the results of C of A repair in patients >1 year of age, because problems in patients operated on during the first year of life, especially in relation to associated congenital cardiac anomalies and recoarctation, make this group best analyzed separately.

The hospital mortality and morbidity of C of A repair beyond infancy have been low.[14–16] The incidence of late mortality and morbidity can be expected to vary depending on the proportion of hospital survivors reviewed and the duration of follow-up. We were able to ascertain the late outcome in all but 1 patient. There was no significant difference in late actuarial survival in patients operated on in individual decades up to the fourth, but late survival more closely approximated that of a general male population when operation was performed before age 20 (Table V) and differed significantly from the general population when operation was performed after age 40.

Late death from cardiovascular disease is well recognized in patients after repair of C of A, and when follow-up extends at least 10 years postoperatively, its incidence is about 10%.[2–4] Eighty to 90% of these deaths are due to cardiovascular disease, the approximate distributions being 30% from aortic valve disease, 30% from coronary artery disease (based on the presumption that patients who die suddenly probably die from this cause although an alternative would be unrecognized aortic rupture), 15% from complications related to the operative site or proximal aortic dissection, and 15% from other cardiovascular disease including intracranial hemorrhage. Like Maron et al[3] we found that the mean age at operation of those who died late was significantly higher than that of long-term survivors. Because the divergence of death rate from normal was increasingly more marked with increasing age at operation beyond 20 years, this is likely due to the prolonged effects of C of A.

Hypertension has been recognized in the absence of recoarctation in late survivors.[2,3,17] Its incidence will vary according to the criteria used. We elected to use the World Health Organization criteria (≥160 mm Hg systolic, ≥95 mm Hg diastolic), because these criteria are unlikely to overestimate the incidence of hypertension in the age groups studied, are widely used in population studies, and in patients <19 years the Task Force Standards[6] to categorize those with pressures >95th percentile as hypertensive rather than >90th percentile as others have done.[18,19]

Our data indicate that the incidence of hypertension varies with the duration of follow-up. Blood pressure tends to decrease in the first few postoperative years, with most patients being normotensive 5 to 10 years after operation, but to increase in later years, and this pattern is similar regardless of age at operation. Not surprisingly, the incidence of late hypertension varies widely in series in which follow-up varies from 1 to many years postoperatively.[5,18] When follow-up was relatively long, the reported incidence was high (24 to 33%).[2,3] Late hypertension was more common in our patients when operation was delayed until after age 20 and this was also found by Menasche et al,[4] but it does occur in patients operated on in their first decade as shown by our study and those of others.[17–19] Whether the incidence of hypertension will be reduced by earlier operation remains unproved. We have followed up 18 patients (not all of whom are in this study) aged 0 to 4 years at operation and without residual coarctation for at least 10 years, 6 remaining at risk 20 years postoperatively. Two became hypertensive at 13 and 18 years. Actuarially, this group is no different from the 5 to 9-year-old group, but no firm conclusions can be drawn from such small numbers.

Coarctation may recur, but some cases are more properly termed *residual coarctation* when they are noted early postoperatively. The incidence varies, depending partly on the method used to evaluate the re-

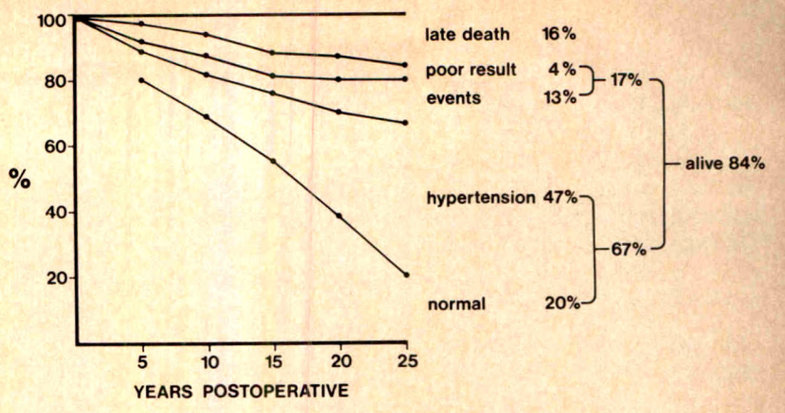

FIGURE 6. Cumulative actuarial curves summarizing overall results.

pair and the pressure gradient chosen.[3,17,20] Using a gradient >20 mm Hg, "recoarctation" was noted in only 4 (3.3%) of the 120 patients who had resection and end-to-end anastomosis and was more frequent when the lesion could not be dealt with in this manner (17.5%).

The relation between BP, especially with exercise, and the adequacy of the surgical repair is complex and not well understood. Different types of exercise testing have been used in patients after C of A repair, most examining the effect of maximal or submaximal exertion.[21–24] Blood pressure has been measured in the arm[21–26] and also in the leg in some cases.[22–26] In general postcoarctectomy subjects tend to have higher arm BP at rest than do control subjects, and the difference is more marked with exercise. It has been suggested that the response of the blood pressure to exercise may indicate an unsatisfactory surgical repair and highlight abnormal gradients between arm and leg pressures not apparent in the resting state.[22,24–26] The need to measure limb BP simultaneously using the same technique has been emphasized.[26] It is also important to note whether BP is measured during or after exercise. When exercise is discontinued, arm BP may decrease promptly (within 10 to 30 seconds),[19,27,28] the decrease tending to be more marked after higher levels of activity.[27] If we had only measured arm BP after the cessation of exercise, values lower than those during maximal exertion would have been recorded in a number of patients (Fig. 4). The response to exercise is also altered by antihypertensive agents.[28,29]

It is difficult to adequately assess the significance of blood pressure measurements in the absence of information concerning the anatomy of the anastomotic area, and like others we have not routinely undertaken aortography in our patients. In acute experiments, reduction of the cross-sectional area of the aortic lumen to 45 to 55% of normal produced a gradient across the constricted area.[30] In postoperative patients Frederickson and Jagt[31] and Frederickson[32] noted that a resting peak systolic gradient across the anastomosis was absent or <10 mm Hg when the anastomotic area was ≥40% of the descending aorta. There is not a consistent relation between central aortic pressures[31,32] or anastomotic width[23] and upper and lower limb pressures at rest or during maximal exercise.

This study gives an overall picture of the long-term outcome after coarctation repair as judged by usual clinical methods. The reason for the recrudescence of hypertension late postoperatively is not clear. In some patients the anastomotic area may be less than ideal, even though BP at rest is normal and a gradient between arm and leg pressures absent. In others the presence of a small gradient probably reflects some restriction at the site of the anastomosis. Our data do not allow firm conclusions about the contribution of anastomotic narrowing to late hypertension, which, however, was not more common in patients with only a satisfactory as compared with a good repair, or when there was a small (versus absent) resting gradient at cardiac catheterization. The effect of the type of repair on pulse wave dynamics and late hypertension cannot be determined at this time. Hansen et al[23] in cineangiographic studies after resection and end-to-end anastomosis noted the aortic wall near the anastomosis appeared stiff in most patients, but in some it was smooth with clearly visible pulsations. Thus, it is possible that narrowing or poor function of the anastomotic area may result in resting hypertension or an exaggerated response of upper limb systolic pressure to exercise. The similar postoperative pattern of BP behavior in patients of differing ages at operation (Fig. 2) does suggest that other factors may be involved. Animal studies indicate that the effects of transient hypertension are not totally reversible,[33,34] and it may be that late hypertension in patients is at least in part due to changes in the arterial wall related to high preoperative pressures which do not completely resolve despite adequate relief of the obstruction. Our data show that it is advantageous for C of A to be repaired before 20 years of age when both late survival and late hypertension are considered. Although it is likely that repair is better undertaken in the first rather than in the second decade of life, clear-cut differences were not demonstrated in this small group of patients.

The optimal age for elective C of A repair is not known.[18] Residual and recurrent C of A is more common when operation is undertaken in the first year of life.[17]

In this series, which does not include patients <1 year of age, the incidence of recoarctation was similar through each decade. Elective operation may be undertaken at 6 to 12 months of age, but long-term data to support this view are not yet available.[35]

The methods described in this study provide an approach to analysis of late results of repair in different age groups at similar times postoperatively and to assessing changes that occur with time. They are applicable in younger age groups not encompassed by this investigation.

Acknowledgment: We thank the many physicians who provided postoperative data on patients and without whose help the study could not have been completed.

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The Valve of the Foramen Ovale in Interatrial Right-to-Left Shunt: Echocardiographic Cineangiocardiographic and Hemodynamic Observations

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In postpartum persistent right-to-left shunt at the atrial level, the valve of the foramen ovale fails to close. As a thin valve-flap the septum primum is pushed to the left during the phases of right atrial pressure predominance and closes to the septum secundum, when left atrial pressure exceeds right atrial pressure. Thus, it performs a marked movement during the cardiac cycle, reflecting the interatrial pressure-flow dynamics. With use of M-mode echocardiography, this movement pattern was studied in 24 patients: 13 with cyanotic heart disease (age 2 days to 21 years) and 11 newborns with persistent transatrial right-to-left shunt due to noncardiac disease. Cardiac defects were confirmed by cardiac catheterization and cineangiocardiography. Interatrial right-to-left shunts were proved by M-mode and 2-dimensional contrast echocardiography. The comparison of the M-mode echocardiographic findings in our patient groups with normal atrial septal movement studied in 20 healthy infants and children revealed considerable differences. The characteristic movement of the valve of the foramen ovale also was compared with results obtained by cineangiography and 2-dimensional echocardiography. Analysis of interatrial blood pressure difference provided a pathophysiologic explanation of the septum primum movement in transatrial right-to-left shunt.

Recently we detected a peculiar structure within the left atrium in the M-mode echocardiogram of a newborn with tricuspid atresia. We suspected that the origin of these echoes could have been the valve of the foramen ovale. This valve is formed by a part of the atrial septum, the septum primum. In the late fetal life, blood entering the right atrium by the inferior vena cava pushes the thin septum primum to the left and passes below the thick margin of the septum secundum into the left atrium. The movement pattern of the valve of the foramen ovale recorded by M-mode echocardiography reflects interatrial pressure-flow dynamics. In cases of postpartum persistent interatrial right-to-left shunt, a persistent fetal movement pattern of the valve of the foramen ovale can be a diagnostic help in the analysis of interatrial hemodynamics.

Methods

Patients: Because we identified the valve of the foramen ovale by M-mode echocardiography for the first time in 1979, we subsequently investigated all our patients with known interatrial right-to-left shunts due to different congenital heart diseases (Group 1, n = 13). Included in this group is the retrospective analysis of the M-mode tracings of 2 patients with total anomalous pulmonary venous connection. In addition, we looked at all newborns with suspected interatrial right-to-left shunts, as discriminated by inhaling 100% oxygen after ruling out structural heart diseases by 2-dimensional (2-D) echocardiography (Group 2, n = 11). This group was labeled as having persistent fetal circulation at the atrial level. Interatrial septal motion as recorded by M-mode and 2-D echocardiography was compared with the findings in 20 normal infants and children (Group 3) and with that in a 38-week fetus intrauterine with atrial tachycardia.

Among the 13 patients in Group 1, 7 had tricuspid atresia of various types, 2 had pulmonic atresia and intact ventricular septum, 3 had total anomalous pulmonary venous connection of the cardiac type without obstruction, and 1 newborn had transient tricuspid regurgitation. Three patients with tricuspid atresia (type B) underwent an aortopulmonary anastomosis, and 1 with tricuspid atresia (type A) had a pulmonary trunk banding. The remaining 7 patients had no previous palliative procedures. Among the 11 newborns in Group 2, 1 had a hepatic arteriovenous fistula, and 10 had such primary lung diseases as pneumonia, respiratory distress syndrome, and aspiration of amniotic fluid; 2 had undergone ligation of a persistent ductus arteriosus, whereas 4 had a significant ductal left-to-right shunt at the time of investigation as confirmed by aortography.

Methods: Table I summarizes the diagnostic methods used in the patients in the 3 groups, not including the 38-week fetus investigated by M-mode and 2-D echocardiography. M-mode echocardiography was done using an Echo IV Electronics for

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TABLE I Diagnostic Methods Used in the 3 Groups

	Group I: Congenital Heart Disease (n = 13)	Group 2: Persistent Fetal Circulation (n = 11)	Group 3: Control (n = 20)
Age			
Range	1–21 days	2–10 days	2 days–8 years
Median	10 days	5 days	4 months
M-mode echocardiography	13	11	20
M-mode + contrast	5	11	3
Two-D echocardiography	11	11	20
Two-D + contrast	6	11	3
Interatrial blood pressure difference (mm Hg)	2	0	0

Medicine instrument with transducer frequencies of 2.5, 3.5, and 5 MHz depending on the patient's weight. On the basis of our experience with 2-D echocardiography and the anatomy of normal hearts, we usually chose the subcostal approach for the detection of the atrial septum in M-mode echocardiography. Only in cases of hypoplastic right ventricle and right atrial enlargement was recording done with a left or right parasternal transducer position. A sweep from the atrial septum to mitral valve was obtained in all patients studied by M-mode echocardiography with either subcostal or parasternal transducer position. Using stop-frame technique in 2-D echocardiography, we reevaluated our M-mode echocardiograms.

Two-D echocardiograms were performed with a mechanical sector scanner (Advanced Technical Laboratories) with 90° wide angle transducers of 3.5 and 5 MHz. Investigations were recorded on a video tape for later evaluation. For contrast echocardiography, 1 to 5 ml of 0.9% sodium chloride was injected into a peripheral vein draining to the superior vena cava. All cardiac defects were confirmed by cardiac catheterization and cineangiocardiography.

Lateral cineangiocardiography was used to analyze atrial septal motion in a patient with tricuspid atresia, type 2B. The frame-rate was 50/s after the injection of contrast medium into the right atrium. Individual pulses of the cineangiographic frames were recorded with the electrocardiogram. This protocol allowed later identification of the single frames. In 1 newborn with pulmonic atresia and intact ventricular septum and in a second with tricuspid atresia, type 2B, we superimposed graphically left and right atrial pressure diagrams, which were recorded during catheter withdrawal from the left to the right atrium. Care was taken in this correlation to ensure that the heart rate remained constant by measurement of the R-R intervals and that pressure tracings were analyzed during identical phases of the respiratory cycle. The resulting pressure-difference diagrams were compared with the atrial-septum movement of the patients as recorded by M-mode echocardiography using the electrocardiogram as the common time base.

Results

Detection and movement of the valve of the foramen ovale in M-mode echocardiography: The atrial septum could be recorded with sufficient quality in all patients entered in the study. In normal hearts the atrial septum performs a smooth sine-wave movement.[1] Its maximal motion is toward the left atrium in early systole and to the right atrium in end-diastole. This pattern was recorded in all our patients in the control group (Group 3) (Fig. 1). In all but 1 patient in Groups 1 and 2 we observed a different and characteristic movement of the atrial septum which will be confirmed later to reflect the movement of the valve of the foramen

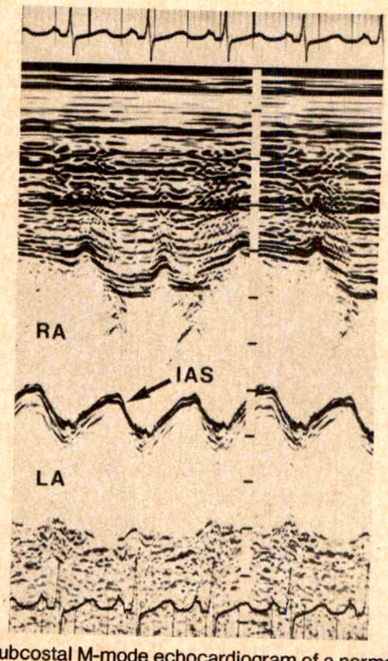

FIGURE 1. Subcostal M-mode echocardiogram of a normal child. The ultrasonic beam crosses the right atrium, the atrial septum, and below the left atrium. IAS = interatrial septum; LA = left atrium; RA = right atrium.

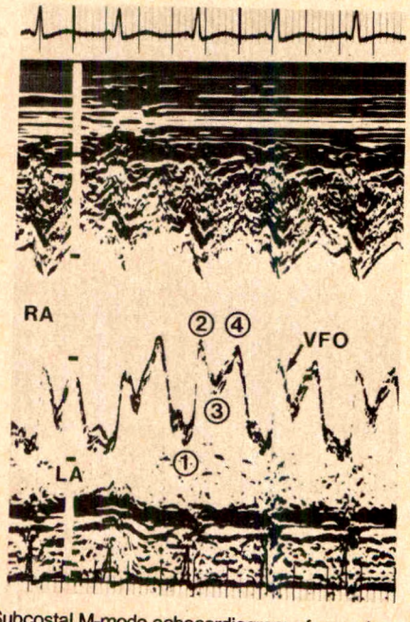

FIGURE 2. Subcostal M-mode echocardiogram of a newborn infant with tricuspid atresia, type 2B. The ultrasonic beam direction is identical to that in Figure 1. VFO = valve of the foramen ovale (see text for explanation of numbers); other abbreviations as in Figure 1.

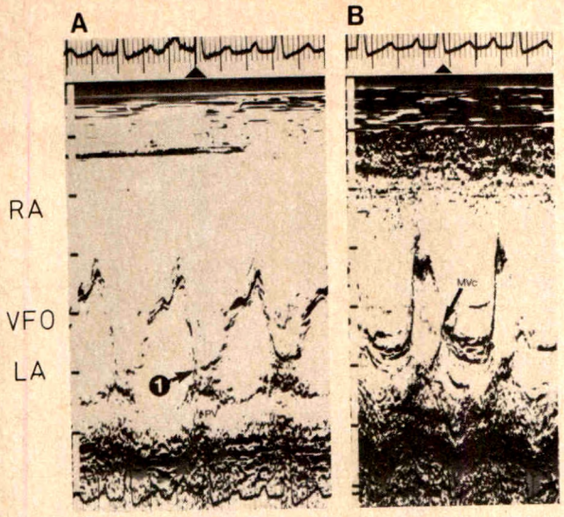

FIGURE 3. A, M-mode echocardiographic recording of the valve of the foramen ovale in a child with tricuspid atresia, type 1A. **B,** recording of the mitral valve in the same patient. The point of the maximal opening of the valve of the foramen ovale (point 1, Fig. 2) and the mitral valve closure were synchronized with the electrocardiogram (**solid triangles**). LV = left ventricle; MVc = mitral valve closure; 1 = maximal opening of the valve of the foramen ovale; other abbreviations as before. PV = pulmonary vein.

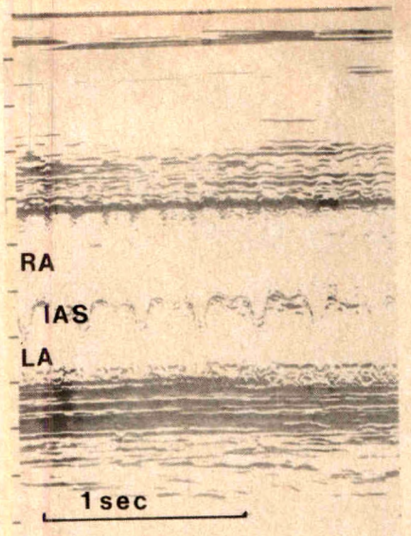

FIGURE 4. M-mode echocardiogram of a 38-week fetus intrauterine. Right atrial contraction indicates atrial flutter at 400 beats/min. Abbreviations as before.

ovale (Fig. 2). With the onset of ventricular systole (R wave in the electrocardiogram), the valve of the foramen ovale has its maximal elongation toward the left atrial posterior wall (point 1). This is followed by a rapid anterior movement during early ventricular systole. From this position (point 2), the valve turns back toward the left atrium in end-systole (point 3). A second anterior movement to point 4 follows. This point appears before the P wave on the electrocardiogram. The cycle ends with a mid- to end-diastolic backward movement, again reaching the starting point 1. This point occurs clearly before closure of the mitral valve (Fig. 3). This movement pattern was recorded with little variation in all the patients in Groups 1 and 2 except 1 newborn infant. In this patient with total anomalous pulmonary venous connection, we failed to detect the valve of the foramen ovale. Operation and autopsy revealed a large atrial septal defect with the size of septum primum and septum secundum markedly reduced.

The intrauterine M-mode echocardiogram of the 38-week fetus also showed the valve of the foramen ovale in a similar pattern as described previously. In this fetus with atrial tachycardia and 2:1 atrioventricular conduction, the elongation of the valve of the foramen ovale altered every second atrial contraction, presumably with respect to ventricular filling (Fig. 4).

The valve of the foramen ovale in 2-D echocardiography: No patient studied was omitted because of poor recording of the atrial septum. In patients in the control group (Group 3) we could not recognize any specific movement patterns of the atrial septum during the cardiac cycle. It was either straight or bulged slightly toward the left or to the right atrium. Even a rhythmic motion of the septum primum away from the septum secundum depending on the respiratory cycle as described by Biermann and Williams[2] could not be observed. However, in the patients in Groups 1 and 2 we recorded a vigorous motion of the septum primum within the cardiac cycle (Fig. 5). As confirmed by slow-motion and frame-to-frame analysis, it consisted of a biphasic opening and closure of the flap. With respect to the electrocardiogram, the opening positions

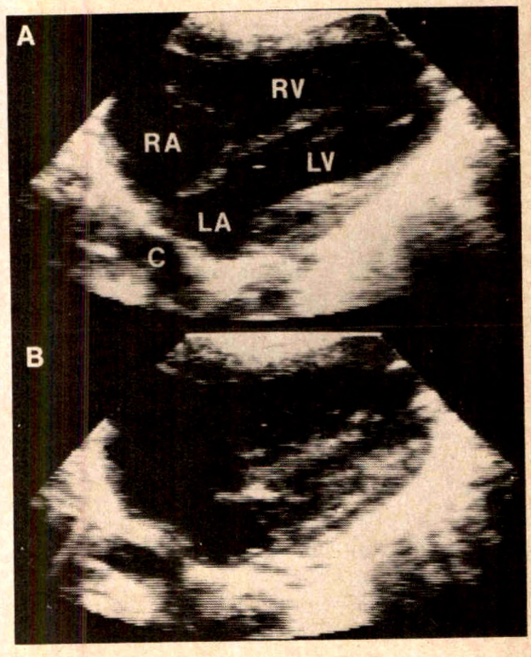

FIGURE 5. Subcostal 2-D echocardiogram of a newborn infant with total anomalous pulmonary venous return. **A,** an apparently intact interatrial septum in diastole. **B,** a systolic frame where an atrial septal defect seems present. C = pulmonary-venous confluence; RV = right ventricle; other abbreviations as before.

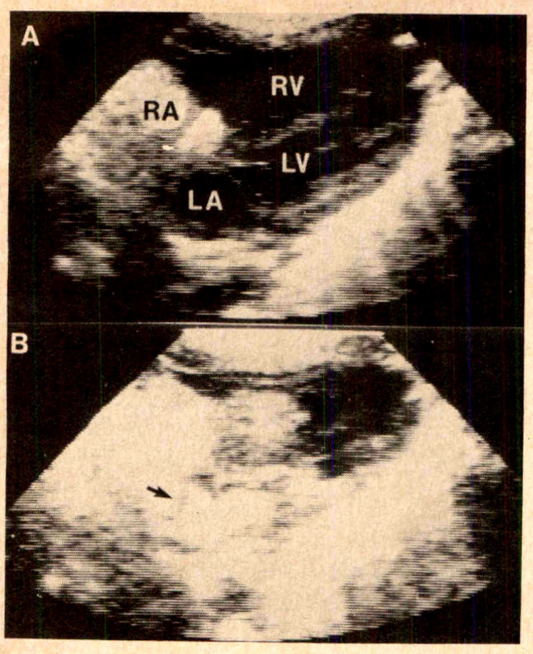

FIGURE 6. Subcostal 2-D echocardiogram of the same patient as in Figure 5 after injection of 0.9% sodium chloride into a peripheral vein. **A,** appearance of the contrast cloud in the right atrial cavity soon after injection. The valve of the foramen ovale was still closed. **B,** the valve of the foramen ovale was open (**arrow**) and the contrast medium consecutively flowed to the left atrium and to the left ventricle. Abbreviations as before.

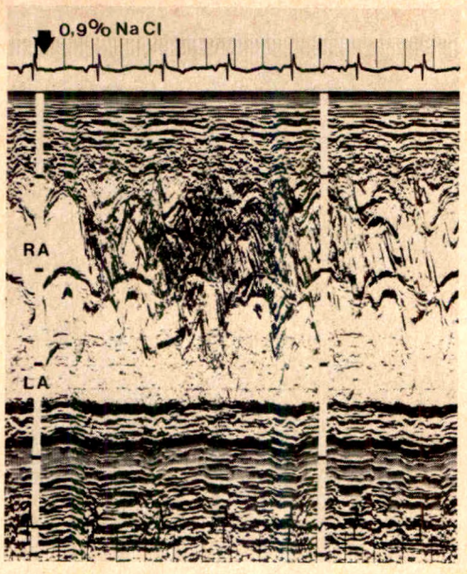

FIGURE 7. M-mode echocardiogram of a newborn infant with pneumonia and interatrial right-to-left shunt. Subcostal transducer position with an ultrasonic beam direction identical to that in Figure 1. After injection of 0.9% sodium chloride into a peripheral vein, the contrast cloud appeared within the right atrium. It was subsequently observed within the left atrium (**arrow**). Abbreviations as before.

corresponded to points 1 and 3 and the closure positions to points 2 and 4 of the aforementioned M-mode echocardiographic findings (Fig. 2).

Contrast echocardiography: In all 17 patients in Groups 1 and 2 studied with 2-D contrast echocardiography, an interatrial right-to-left shunt could be observed in the subcostal 4-chamber view (Fig. 6), whereas in the control group (Group 3) no shunt was present.

In M-mode contrast echocardiography, the right atrial contrast filling phase could be observed with the transducer in a subcostal position. With respect to the electrocardiogram, the contrast material subsequently appeared within the left atrium at the very same moment, when the valve of the foramen ovale opens (Fig. 7).

The valve of the foramen ovale in cineangiocardiography: In 1 of the patients in Group 1 with tricuspid atresia type 2B, we were able to demonstrate the valve of the foramen ovale by cineangiocardiography in the lateral view. After right atrial contrast injection a vigorous movement of the septum primum was seen. This led to a rhythmic opening and closure of the foramen ovale, allowing contrast medium to pass into the left atrium. With respect to the electrocardiogram, opening and closure of the foramen ovale had the same timing as seen in the M-mode echocardiogram.

Interatrial blood pressure differences: The interatrial pressure difference diagram obtained in 2 newborns in Group 1 showed a striking similarity to the movement of the valve of the foramen ovale recorded in M-mode echocardiography. In the patient with tricuspid atresia a mean interatrial pressure difference of 4 mm Hg indicated a restrictive foramen ovale; in the second patient, the mean interatrial pressure difference was 1.5 to 2 mm Hg. The opening of the valve of the foramen ovale occurred when right atrial pressure exceeded the left side in early diastole. The moment clearly occurs before the P wave on the electrocardiogram and the apex of the right atrial A wave. The following closure of the flap in early systole and its slighter reopening and final closure can also be correlated to the instantaneous pressure predominances favoring either the left or the right side (Fig. 8).

Discussion

The valve of the foramen ovale is identical to the ventrocephalic free margin of the septum primum. In all cases of interatrial right-to-left shunt through a patent foramen ovale (whether intrauterine or postpartal), the blood flow pushes the thin septum primum to the left and passes below the thick dorsocaudal margin of the septum secundum into the left atrium. It does not make any difference whether the interatrial right-to-left shunt is dependent on a defect or functional. Postpartum there are many hemodynamic situations that can lead to a persistent interatrial right-to-left shunt. Usually there are anatomic or functional right heart obstructions, mainly accompanied by a more or less reduced right ventricular compliance or right atrial volume overload.

Our study in 24 patients demonstrates that the movement of the valve of the foramen ovale in cases of interatrial right-to-left shunt can be visualized by M-mode echocardiography. The tracing is markedly dif-

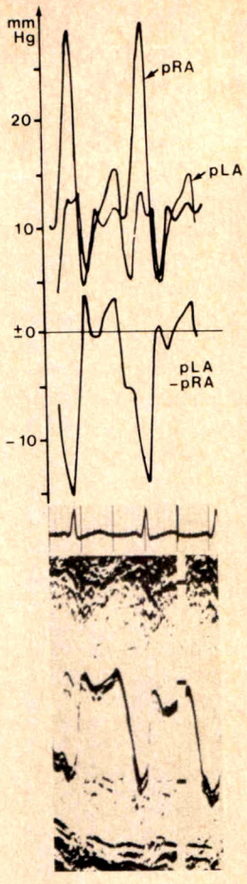

FIGURE 8. Comparison of the interatrial pressure difference with the movement of the valve of the foramen ovale in the subcostal M-mode echocardiogram of an infant with tricuspid atresia, type 2B. The single traces were synchronized to the electrocardiogram. pLA = left atrial pressure; pLA-pRA = interatrial pressure difference; pRA = right atrial pressure.

ferent from the atrial septum movement recorded in normal patients and similar to the findings in an intrauterine fetus.

There are few reports describing the movement of the valve of the foramen ovale by M-mode echocardiography. Schmaltz and Apitz[3] described an unusual left atrial echo in a newborn with hypoplastic right heart. They could not relate the echo to any structure of the heart. The reported tracings, however, were identical to those we found when studying the valve of the foramen ovale. Silvermann et al[4] reported a similar echo in a newborn with tricuspid atresia. They could exclude its origin from any right ventricular or right atrial structure. A corresponding report was given by Bini et al[5] in a case of tricuspid atresia. These investigators suggested that the only intracardiac structure capable of simulating a tricuspid valve movement was the valve of the foramen ovale. This hypothesis has not yet been proved sufficiently. Former observations by Biermann and Williams[2] described a rhythmic removal of the septum primum from the septum secundum depending on the respiratory phase using 2-D echocardiography. Their studies were not aimed at studying the typical movement of the valve of the foramen ovale in interatrial right-to-left shunt. Tei et al[6] described the atrial septum position and estimated thickness of the septum in 29 patients with right or left atrial overload using M-mode echocardiography. In this study there was also no description of the atrial septum movement. The M-mode echocardiographic tracing of an atrial septal aneurysm in an infant with hypoplastic right heart syndrome reported by Sahn et al[7] was identical to the movement of the valve of the foramen ovale in our patients, and a recent report of Reder et al[8] on this feature confirmed these findings. However, in our patients there was no evidence of atrial septal aneurysm as shown by 2-D echocardiography, cineangiography, or later operation.

Marked movement of the valve of the foramen ovale is a newly described tracing in M-mode echocardiography. By comparing this tracing with different diagnostic methods such as 2-D echocardiography and cineangiocardiography, we could be certain that the M-mode echoes described in fact originate from a vigorously active valve of the foramen ovale. It could be confirmed that the elongations toward the left atrium (points 1 and 3, Fig. 1) represent an opening of the flap, whereas the elongations toward the right atrium (points 2 and 4) are closure positions. This movement is passive and caused by the interatrial pressure-flow dynamics, as shown by comparison with atrial pressure tracings in 2 patients (1 with absent right atrioventricular connection and the other with a low-compliance right ventricle). Right atrial pressure dominance and subsequent interatrial right-to-left shunting occurs twice within the cardiac cycle: first, in early diastole probably because of absent or reduced right ventricular filling; and second, in systole because of a slightly more rapid pressure increase in the right atrial V wave than in the left. The 2 points of left atrial pressure predominance (points 2 and 4, Fig. 2) can be attributed to somewhat higher pressures of left atrial X and V waves. The closure of the mitral valve coincides in time with the decrease of the right atrial pressure dominance (Fig. 3 and 8), thus indicating the dependence of interatrial right-to-left shunting on the left ventricular filling.

As similar movement patterns of the valve of the foramen ovale were recorded by M-mode echocardiography in all patients in Groups 1 and 2, one can presume that the shunting dynamics were also similar in all, even though the individual hemodynamic situation differed considerably. Reduced or absent right ventricular compliance can only provide an explanation for the shunt dynamics in cases of tricuspid atresia and pulmonic atresia with intact ventricular septum. In the patient with tricuspid regurgitation and in those with total anomalous pulmonary venous connection, right atrial volume overload must be considered to effect interatrial right-to-left shunts. A similar condition can be assumed in the newborn with a systemic left-to-right shunt through a hepatic arteriovenous fistula. In these patients right ventricular compliance is probably normal, but not high enough to allow the increased right atrial volume to pass completely through the tricuspid valve.

In the 38-week fetus the commonly accepted explanation that the flow predominance of blood entering the right atrium through the inferior vena cava leads to the fetal right-to-left shunt at atrial level cannot be accepted entirely. This fetus had atrial tachycardia with 2:1 atrioventricular conduction. Biphasic opening of the valve of the foramen ovale indicates that a major interatrial right-to-left shunt occurs every second atrial contraction. One can therefore assume that the interatrial shunt depends more on the ventricular filling than on the venous blood flow dynamics.

In the newborns in Group 2 with primary lung disease and atrial right-to-left shunt, the interatrial hemodynamic features are poorly understood. The similarity of their foramen ovale valve movement in M-mode echocardiography leads to the assumption that the interatrial pressure-flow dynamic features are similar to those in the patients with cyanotic heart defects studied in Group 1. This is difficult to accept, because at least in the 4 patients with proven significant ductal left-to-right shunt, a left atrial volume overload should have been present. A markedly different ventricular compliance favoring the left side may provide a hypothetical explanation, which needs support by further hemodynamic studies.

Conclusion: The valve of the foramen ovale can be recorded by M-mode echocardiography in patients with interatrial right-to-left shunt. The sensitivity of this pattern was high in our patients as controlled by contrast echocardiography or cineangiocardiography. Specificity could not be tested accurately, as we did not investigate patients with right atrial pressure or volume overload having a foramen ovale that was not patent. In 1 patient with total anomalous pulmonary venous connection and a large atrial septal defect, we failed to record the expected movement of the septum primum.

Being a thin membrane, the foramen ovale flap easily follows interatrial pressure-flow changes. Thus its movement reflects very accurately the interatrial pressure-flow dynamics. Despite the different hemodynamic situations in all patients with atrial right-to-left shunt, the striking similarity of their foramen ovale flap movements indicates a similarity in atrial right-to-left shunt timing within the cardiac cycle. Interatrial shunt dynamics, however, may mainly depend on the ventricular filling capacities, irrespective of whether the shunt is dependent on a cardiac or a functional defect.

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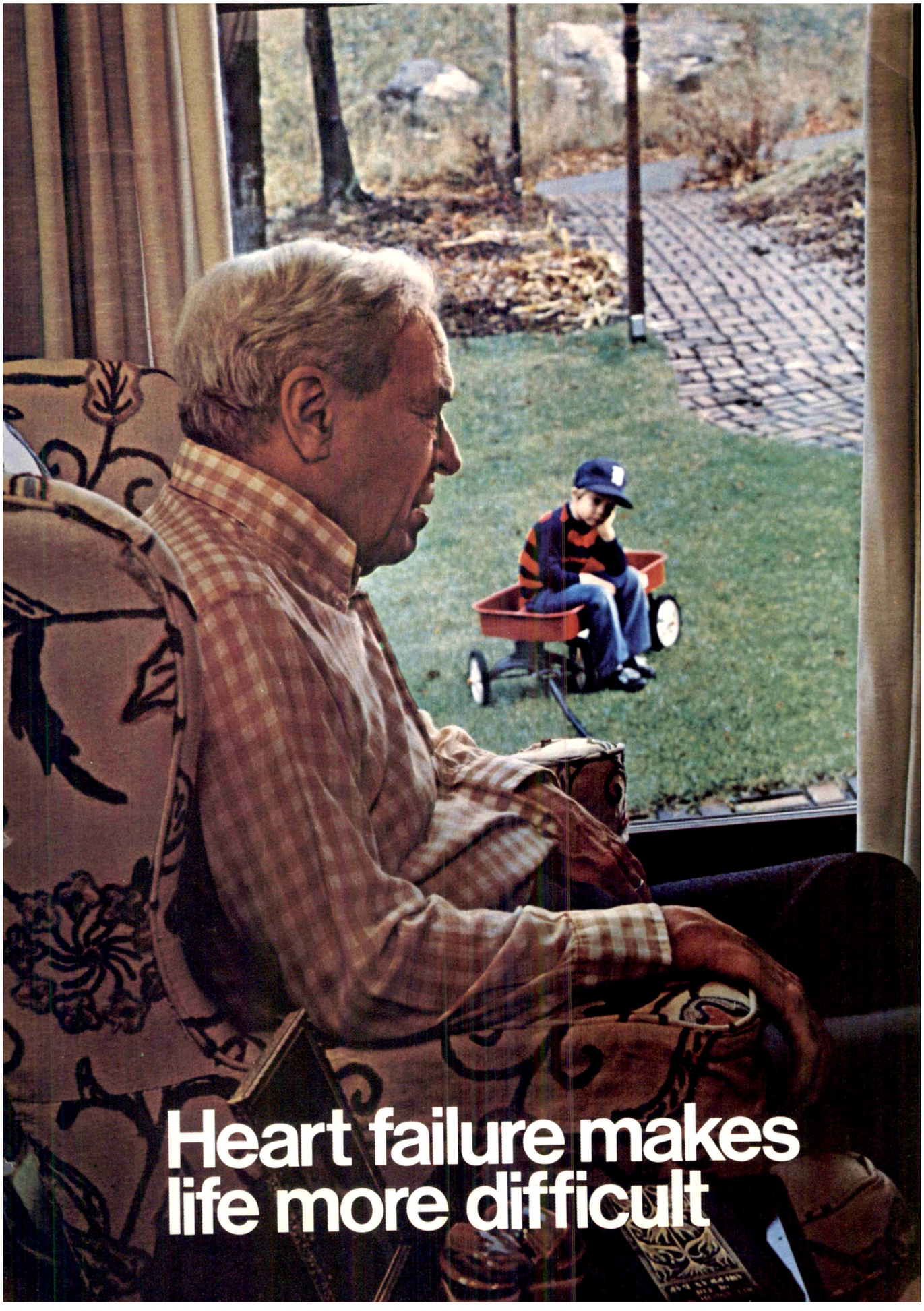
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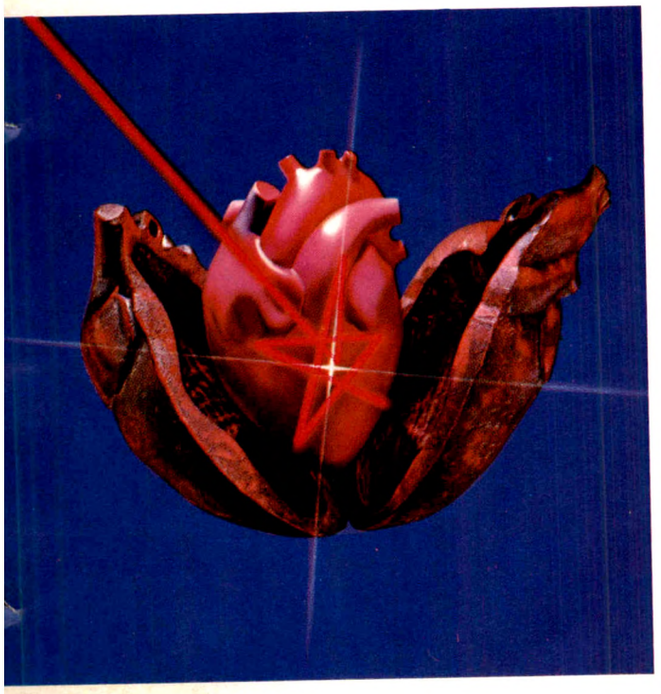

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CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

*Angiotensin Converting Enzyme

†Please see brief summary of prescribing information on last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Data on file, Squibb Institute for Medical Research.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.
Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.
Agents Causing Renin Release — Captopril's effect will be augmented by

 (Continued on next page.)

(continued from preceding page)

antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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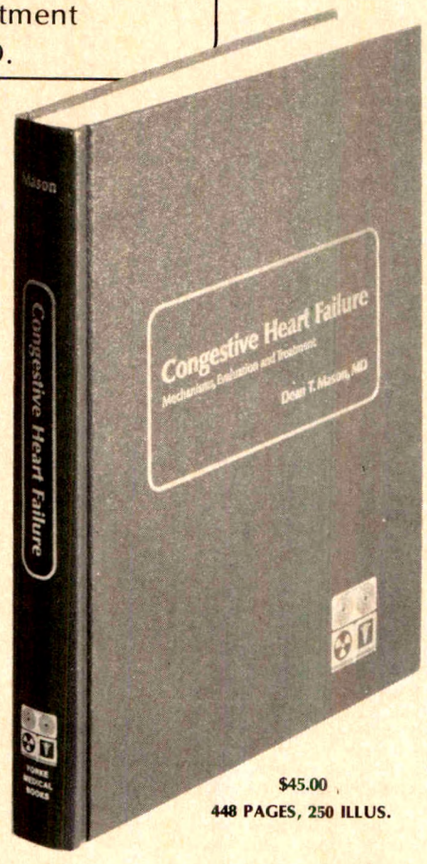
Congestive Heart Failure

Mechanisms, Evaluation and Treatment

Dean T. Mason, M.D.



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Immediate Past President, American College of Cardiology

Member of the American Board of Internal Medicine Cardiovascular Diseases

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Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

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Management of Adults With Congenital Bidirectional Cardiac Shunts, Cyanosis, and Pulmonary Vascular Obstruction: Successful Operative Repair in 3 Patients

VERDI J. DiSESA, MD, LAWRENCE H. COHN, MD, and WILLIAM GROSSMAN, MD

Patients with congenital cardiac shunts in whom marked functional disability, cyanosis and pulmonary arterial hypertension develop have been considered inoperable or at exceedingly high risk. Three adult patients, 2 with atrial septal defect (ASD) and 1 with patent ductus arteriosus (PDA), presented with New York Heart Association class IV symptoms, bidirectional shunting with cyanosis, polycythemia, severe pulmonary hypertension, and increased pulmonary vascular resistance. Pulmonary arterial pressure did not decrease in response to administration of 100% oxygen in any patient, and 2 had lung biopsy results showing advanced pulmonary vascular obstruction. While a right-to-left shunt caused cyanosis in all patients, the net shunt was left to right ($Q_p/Q_s > 1$) and the resistance ratio (R_p/R_s) <0.5. All 3 patients survived operation, became acyanotic with normal hematocrit, and are in functional class I or II a mean of 36 months postoperatively. At repeat cardiac catheterization, pulmonary arterial pressure and resistance had decreased substantially.

This high-risk group of patients with bidirectional shunts, in whom cyanosis due to pulmonary vascular obstruction and polycythemia develop and who appear to be at very high operative risk, should still be considered for surgical correction if the usual criteria for operability exist: net left-to-right Q_p/Q_s and R_p/R_s <0.50.

Patients with congenital left-to-right shunts in whom severe functional disability, cyanosis, and pulmonary hypertensive changes in the lungs develop have been considered at high operative risk. In adults, this complex is particularly ominous and often portends Eisenmenger's syndrome with a predominent right-to-left shunt.[1] However, a small group of patients presenting with this clinical syndrome are not inoperable because their *net* shunt remains left to right. Because of the longstanding uncorrected anomaly, they have a significant component of right-to-left shunting producing cyanosis.[2,3] Although simulating Eisenmenger's syndrome clinically, these patients may, in fact, be operated upon and may go on to lead a relatively normal life after precise catheter diagnosis and surgical correction. This report details experience with 3 such patients who appeared inoperable on initial clinical evaluation but who have done well in long-term follow-up after preoperative hemodynamic study and surgical correction.

From the Departments of Surgery and Medicine, Harvard Medical School and the Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by Grant HL 19246 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received December 6, 1982; revised manuscript received January 31, 1983, accepted February 2, 1983.

Address for reprints: Lawrence H. Cohn, MD, Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115.

Clinical Material

These 3 consecutive patients were operated upon between 1977 and 1980. Two patients underwent closure of an atrial septal defect (ASD) and 1 had ligation of a patent ductus arteriosus (PDA). All patients underwent complete cardiac catheterization preoperatively and at least once postoperatively. Oxygen consumption for calculation of cardiac output was measured (not assumed), and pulmonary venous sampling was obtained in the 2 patients with ASD. In all patients, preoperative pulmonary arterial pressures and resistances were evaluated with and without the administration of 100% oxygen for 15 minutes. Other forms of pharmacologic pulmonary vasodilatation such as priscoline or prostacyclin were not administered. Two patients (1 with ASD, 1 with PDA) had concomitant lung biopsies at operation. The pre- and postoperative hemodynamic features are detailed in Table I. Pre- and postoperative chest x-rays of Patients 1 and 2 are shown in Figures 1 and 2.

Discussion

The development of cyanosis due to pulmonary vascular obstruction has long been considered an ominous prognostic sign in patients with a congenital left-to-right

TABLE I Pre- and Postoperative Hemodynamic Findings*

	PA Pressure (mm Hg) S/D	PVR (dynes s cm^{-5})	Q_p/Q_s	R_p/R_s	Aortic Pressure (mm Hg) S/D	Q_s (liters/min)	Arterial Blood O_2 Sat (%)	Hct (%)	Grade Lung Biopsy
Patient 1: 45-Year-Old Man With Patent Ductus Arteriosus (2 cm)									
Preoperative	110/55 (75)†	982	1.8	0.45	120/55 (80)	2.7	86	62	IV
Postoperative									
2 weeks	110/40 (60)	649	1.0	0.65	124/76 (92)	6.2	96	36	. . .
6 months									
Rest	65/25 (40)	464	1.0	0.35	130/70 (90)	5.0	95	42	. . .
Exer	65/15 (35)	278	1.0	0.26	160/75 (97)	6.9	95	. . .	. . .
15 months	50/23 (34)	337	1.0	0.35	105/60 (75)	5.7	95	42	. . .
Patient 2: 31-Year-Old Woman With Atrial Septal Defect (5 × 7 cm)									
Preoperative	100/37 (55)†	735	1.9	0.29	120/75 (95)	2.8	88	54	IV
Postoperative									
3.5 months	58/30 (42)	509	1.0	0.45	120/65 (85)	5.5	98	41	. . .
16 months									
Rest	38/26 (30)	297	1.0	0.26	130/70 (90)	6.2	96	42	. . .
Exer	75/42 (55)	331	1.0	0.31	160/98 (122)	8.7	96	. . .	. . .
Patient 3: 66-Year-Old Woman With Atrial Septal Defect (3 × 6 cm)									
Preoperative	90/30 (50)†	563	1.5	0.31	145/70 (90)	3.3	90	56	. . .
Postoperative	70/30 (40)	350	1.0	. . .	130/70 (80)	3.8	91	40	. . .
1 month (rest)									

* Mean values in parentheses.
† No change with 100% oxygen.
Exer = exercise; Hct = hematocrit; PA = pulmonary artery; PVR = pulmonary vascular resistance; Q_p = pulmonary blood flow; Q_s = systemic blood flow; R_p/R_s = ratio of pulmonary to systemic vascular resistance; S/D = peak systole/end-diastole.

shunt.[1–5] Efforts to develop criteria of operability in these patients have focused on histologic and hemodynamic assessments of the reversibility of pulmonary vascular disease.

Since 1958, when Heath and Edwards[6] described the morphologic changes in the lung in pulmonary hypertension, attempts have been made to correlate pathologic grade with reversibility of disease. Grade IV to VI pulmonary hypertensive changes have been generally considered to be irreversible.[7] Rabinovitch et al[8] and Wagenvoort[9] have recently suggested that analysis of lung biopsies may help determine operability in patients who have severe pulmonary hypertension with histologic pulmonary vascular changes. If irreversible changes are present on biopsy, surgery is not advised. Furthermore, Wagenvoort[9] contends that a 2 × 1 × 1 cm biopsy specimen is representative of the pulmonary vascular disease in the lung as a whole. This amount of lung tissue was available in the biopsies of our 2 patients who had changes of advanced pulmonary vascular obstruction (grade IV).

Other authors have proposed more dynamic tests of the reversibility of pulmonary vascular obstruction. For example, failure of pulmonary arterial pressure and vascular resistance to decrease after breathing 100% oxygen,[10,11] as used in our patients, has been considered a contraindication to surgery. However, all 3 of our patients had nonreversibility of pulmonary hypertension with 100% oxygen.

Despite the clinical appearance of inoperability due to the development of cyanosis and pulmonary hypertension, and failing the 2 aforementioned objective tests of operability, our 3 patients did well after surgical correction. Although all 3 patients had right-to-left shunts sufficient to cause cyanosis and polycythemia,

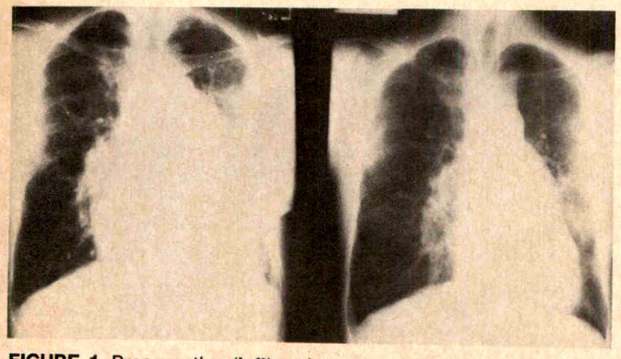

FIGURE 1. Preoperative (**left**) and postoperative (**right**) chest roentgenograms of Patient 1 documenting reduction in cardiomegaly and pulmonary plethora.

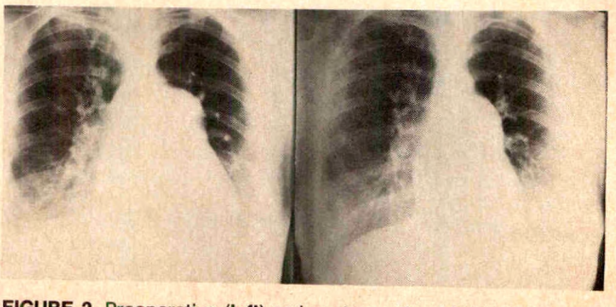

FIGURE 2. Preoperative (**left**) and postoperative (**right**) chest roentgenograms of Patient 2 showing substantial improvement.

the predominant shunt at cardiac catheterization was still left to right ($Q_p/Q_s > 1$). Obviously, when Q_p/Q_s is <1, pulmonary vascular obstruction is too severe to permit surgery. Second, the resistance ratio (R_p/R_s) was <0.5 in all 3 patients. This ratio takes into account miscellaneous factors (catecholamines and blood viscosity) that affect both pulmonary and systemic vascular beds. It therefore eliminates the need for specific corrections for these factors when assessing the severity of intrinsic pulmonary vascular changes.[12,13] These are the 2 key factors in assessing operability.

In addition, systemic arterial desaturation, observed preoperatively in our patients, can itself cause symptoms and hemodynamic abnormalities that exaggerate pulmonary vascular obstruction. Braunwald and Morrow[14] showed that despite persistent pulmonary hypertension after partial shunt closure, patients may have marked symptomatic improvement due to the amelioration of arterial oxygen desaturation alone.

Finally, the decrease in hematocrit and blood viscosity usually seen after elimination of cyanosis has been shown to cause a reduction in both pulmonary arterial pressure and resistance.[15,16] Hemodilution associated with cardiopulmonary bypass and the correction of hematocrit due to elimination of the right-to-left shunt probably contributed significantly to our patients' early clinical response. However, altered blood viscosity alone cannot explain the progressive improvements in pulmonary hemodynamic function that occurred after hematocrit and oxygen saturation had returned to normal.

Acknowledgment: We thank Stephen VanDevanter, MD, who operated on Patient 3 and permitted us to include this patient in our series, Gerald Angoff, MD, who performed postoperative cardiac catheterization on Patient 3, and Barbara Hebert for manuscript preparation.

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Obstruction Within the Right Ventricular Body: Two-Dimensional Echocardiographic Features

LAURA J. Von DOENHOFF, MD and NAVIN C. NANDA, MD

Real-time 2-dimensional (2-D) echocardiograms were performed in 4 patients, all with considerable obstruction within the right ventricular (RV) body, in 3 patients due to muscle bundles and in 1 due to hypertrophic cardiomyopathy (HC). None had obstruction at the pulmonic valve level or immediately below. Echocardiographically, obstruction presented in 3 patients as localized bulging of the RV free wall in the subinfundibular region such that the RV cavity presented a typical "hourglass" appearance. Associated ventricular septal defect (VSD) was detected in 2 patients by echocardiography. In the fourth case, a patient with HC, RV obstruction was associated with a prominent bulge of the ventricular septum into the right ventricle. In 3 patients, the obstruction was convincingly demonstrated only in the subcostal RV inflow-apex-outflow plane, rather than in the standard echocardiographic planes. Pulse Doppler studies in 2 patients demonstrated disturbed RV flow. Obstruction within the RV body is a potentially serious condition which has been overlooked both at cardiac catheterization and at surgery. Demonstration of this lesion by 2-D echocardiography appears feasible and would greatly improve diagnostic accuracy.

Right ventricular (RV) body obstruction, although uncommon, is often surgically remediable. Its clinical diagnosis is difficult since the findings may mimic tetralogy of Fallot or other forms of RV obstruction, and the lesion may coexist with, as well as mimic, ventricular septal defect (VSD)[1,2] and valvular pulmonic stenosis.[3] The diagnosis has occasionally been missed even at cardiac catheterization[2] and at surgery.[3] We report here the first definitive application of real-time 2-dimensional (2-D) echocardiography in the diagnosis of RV obstruction at the subinfundibular level.

Methods

Four patients, 3 male and 1 female, aged 2 to 48 years (Table I) were studied. All had intracavitary RV pressure gradients and evidence of severe discrete RV cavity narrowing at biplane ventriculography. None had evidence of valvular or classic infundibular pulmonic stenosis. All patients underwent 2-D echocardiographic examinations which were performed with an Advanced Technology Laboratories (ATL) wide angle 90° sector scanner using the standard planes. Three of the 4 patients were examined echocardiographically either before or without knowledge of the catheterization findings. The subcostal RV inflow-apex-outflow (IAO) plane, which has proven particularly useful in the study of RV wall motion,[4] also was obtained in 3 patients. In this view, the transducer is pressed firmly into the epigastrium and directed superiorly and somewhat anteriorly so that the ultrasonic beam passes through the diaphragmatic wall to view the tricuspid valve apparatus, the RV apex, and the pulmonic valve (Fig. 1 to 3).

The RV diaphragmatic wall maximal end-diastolic thickness was measured at the onset of the QRS complex in the subcostal 4-chamber plane and was considered to be hypertrophied if the measurement was >5 mm[5]. HC was considered present if the ventricular septal thickness was ≥15 mm, if its ratio to posterior wall thickness was ≥1.5:1, and if narrowing of the left ventricular (LV) outflow tract to <20 mm and prominent systolic anterior motion of the mitral valve also were present.[6]

Pulse Doppler studies were performed in 2 patients using an ATL Mark V Duplex system in which blood flow patterns were sampled in the right ventricle along a cursor line placed on the 2-D image. Disturbed flow was characterized by multiple widely fluctuating frequencies in the Doppler shifts, outlined graphically on the time-interval histogram. All 2-D and Doppler echocardiographic studies were reviewed by 2 independent observers.

Results

The 2 observers agreed in their analysis of the echocardiographic findings which, along with the clinical findings, are summarized in Table I. In all patients the most dramatic finding was the demonstration of marked localized narrowing of the RV subinfundibular area, to one third or less the width of the adjacent cavity. In Patients 1, 2, and 3, there was localized bulging of the RV free wall well below the pulmonic valve in the subinfundibular region, such that the RV cavity presented a typical hourglass appearance. In Patients 1 and 2, this was identified convincingly only in the IAO plane (Fig. 4). In Patient 3, the obstruction was seen from a parasternal oblique short-axis view (Fig. 5) but was not well appreciated in the apical 4-chamber view. The IAO

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TABLE I Summary of Patients' Data

Patient	Age (yr) & Sex	Symptoms, Murmur, Cardiomegaly	Pressure Gradient (mm Hg)		VSD at Cath	Echocardiographic	
			Right Ventricle	Left Ventricle		RVH	VSD
1	48M	0, +, +	25	0	+	+	0
2	2M	N, +, +	33	0	+	+	+
3	18F	0, +, +	58	0	+	+	+
4	27M	+, +, +	60	80	0	+	0

+ = present; 0 = absent; Cath = catheterization; N = not applicable; RVH = right ventricular hypertrophy; VSD = ventricular septal defect.

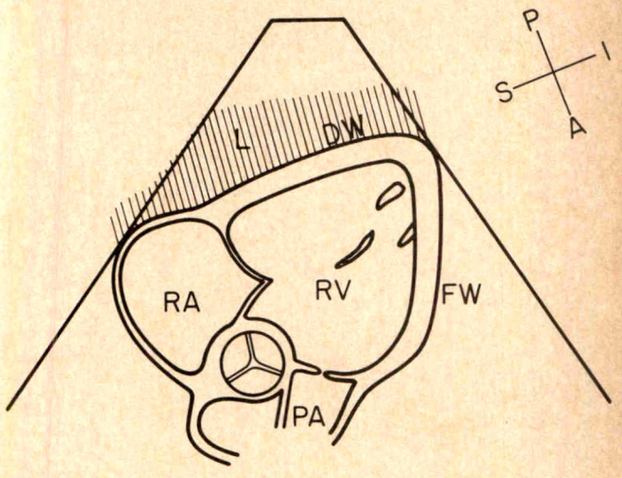

FIGURE 1. Subcostal right ventricular (RV) inflow-apex-outflow plane. In this view, the transducer is pressed firmly into the epigastrium and directed superiorly and somewhat anteriorly so that the ultrasonic beam passes through the diaphragmatic wall (DW) to view the right atrium (RA), tricuspid valve, right ventricle, and RV outflow area. In this plane, the pulmonic valve and pulmonary artery (PA) are relatively anterior (A) as well as superior (S) to the RV DW, and the RA is relatively superior as well as somewhat to the right of the RV apex. The orientation compass is simplified to depict only 4 directions, and they are approximate. FW = free wall; I = inferior; L = liver; P = posterior.

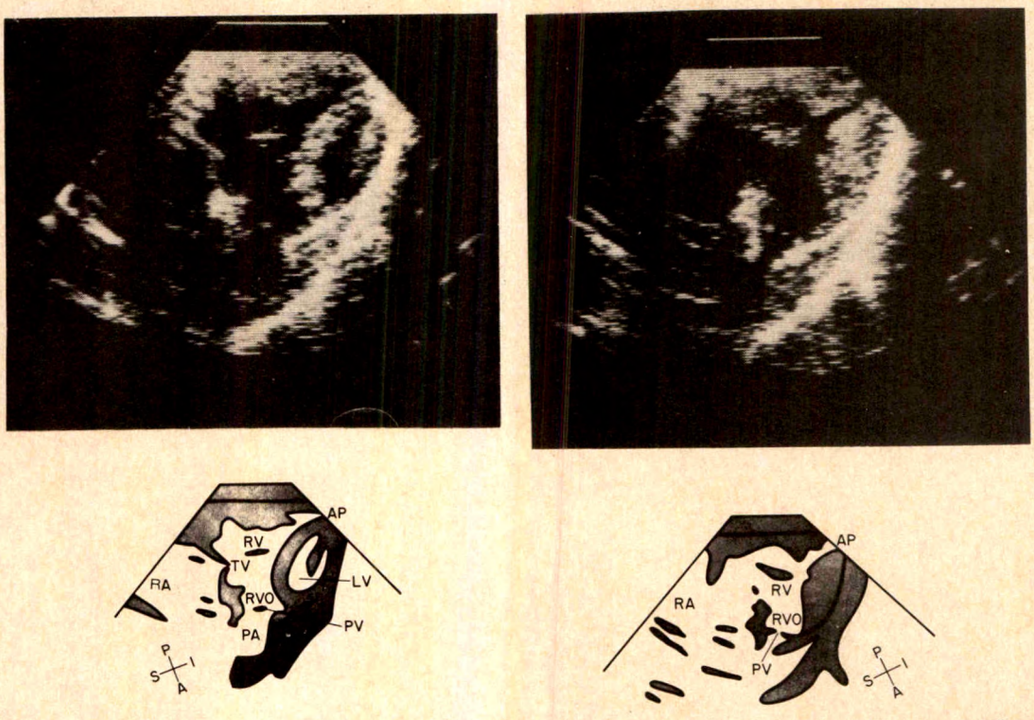

FIGURE 2. Subcostal planes in a normal subject. **Left,** as in Figure 1, the transducer is pressed firmly into the epigastrium and directed superiorly and somewhat anteriorly to display the RA and the right ventricular outflow tract, but it is also directed leftward to display the left ventricle (LV). Septal anatomy can thus be studied. **Right,** as the transducer is rotated in the same patient to exclude the LV from view, the FW of the RV appears and can be studied. Distinction can thus be made between prominences of the right ventricular FW and those of the right side of the septum. The aortic root is not included in this plane. AP = right ventricular apex; PV = pulmonic valve; RVO = right ventricular outflow tract; TV = tricuspid valve. Orientation and other abbreviations as in Figure 1.

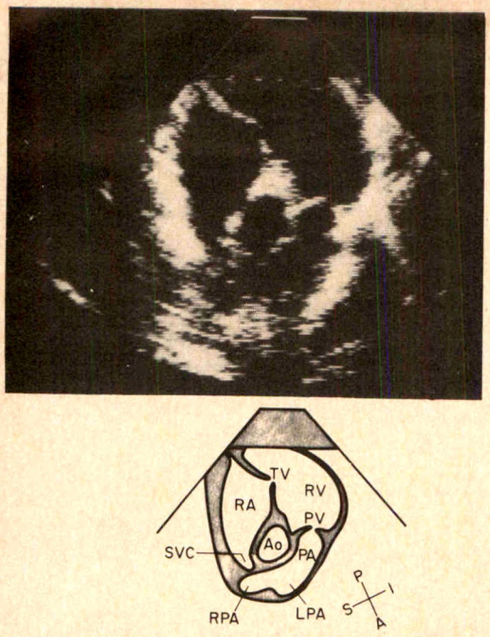

FIGURE 3. The subcostal inflow-apex-outflow plane is best visualized in children and in adult patients with RV dilatation without obstruction. In this adult, the right ventricle is dilated and the RV free wall is normal and creates no narrowing. Ao = aorta; LPA = left pulmonary artery; RPA = right pulmonary artery; SVC = superior vena cava. Orientation and other abbreviations as in Figures 1 and 2.

FIGURE 4. Subcostal inflow-apex-outflow plane in Case 1, a patient with RV subinfundibular obstruction. The free wall bulges markedly into the subinfundibular portion of the right ventricle, creating an hourglass narrowing. On the scale, the distance between 2 of the larger marks represents 10 mm. N = narrowing; RVA = RV apex; RVI = RV inflow area. Orientation and other abbreviations as in Figures 1 to 3.

plane was not obtained in this patient. In Patients 2 and 3, a VSD was observed echocardiographically. In Patient 4, HC was present, and a subinfundibular ventricular septal bulge was seen in the IAO plane, as well as apical RV cavity obliteration in the long-axis plane. In this patient, the ventricular septum was 40 mm thick, the LV posterior wall 10 mm thick, the LV outflow tract was 15 mm wide, and prominent systolic anterior movements of the mitral valve were present.

In both patients in whom pulse Doppler studies were performed (Patients 1 and 4), the time-interval histogram showed disturbed flow when the Doppler sample volume was positioned in the right ventricle. Figure 6 depicts the findings in Patient 1.

All patients had hypertrophy of the RV diaphragmatic wall. None had 2-D echocardiographic systolic doming of the pulmonic valve suggestive of pulmonic valvular stenosis. The pulmonic valve on the M-mode

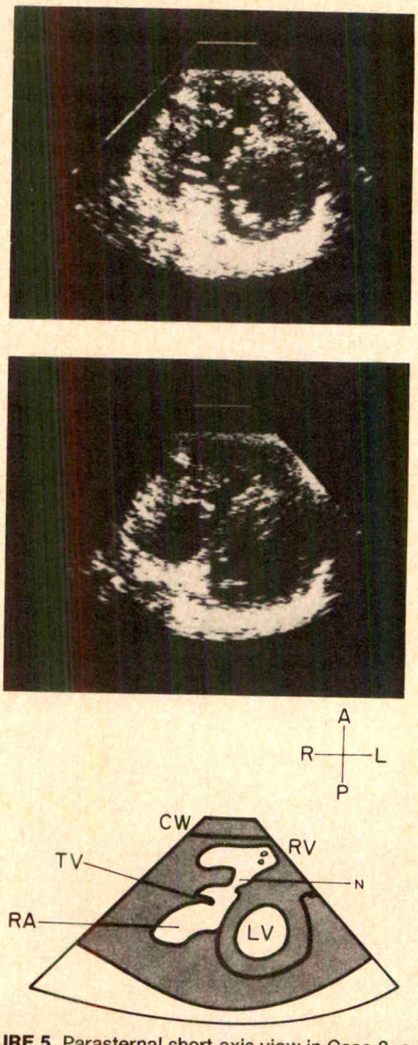

FIGURE 5. Parasternal short-axis view in Case 3, a patient with RV obstruction caused by a finger-like projection from the free wall of the right ventricle. CW = chest wall; L = left; R = right. Other abbreviations as in Figures 1 to 4.

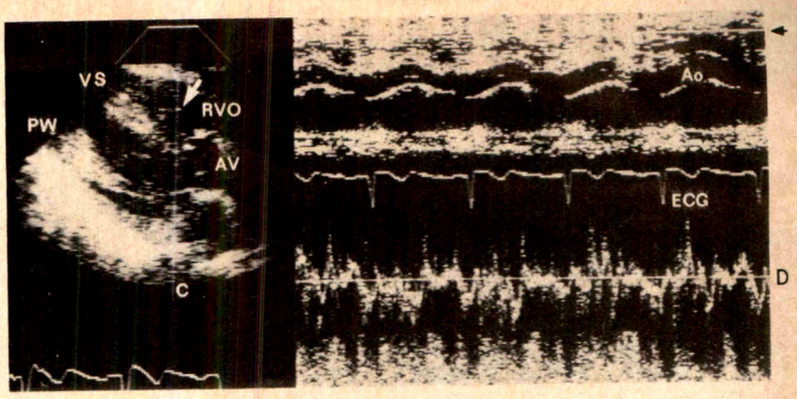

FIGURE 6. Pulse Doppler studies in Case 1, a patient with RV subinfundibular obstruction. **Left panel,** the long-axis view shows the site of the Doppler sample volume within the right ventricle (**white arrow**). **Right panel,** the time-interval histogram demonstrates multiple widely fluctuating frequencies in the Doppler shifts suggestive of disturbed flow. The **black arrow** denotes the sample site in the right ventricle on the M-mode tracing obtained along the cursor line. Ao = left ventricular outflow area; AV = aortic valve; C = cursor line; D = Doppler signals; ECG = electrocardiogram; PW = posterior wall; VS = ventricular septum. Other abbreviations as in Figures 1 to 5.

showed high frequency systolic fluttering in Patients 1, 2, and 3 and midsystolic notching in Patient 1; it was normal in Patient 4.

Discussion

Aberrant RV muscle bands may exist without interfering with flow, particularly if they are small. They may, however, be hypertrophied, and obstruction occurs when sufficiently enlarged muscle bands project into the subinfundibular region and create a pressure gradient.[2] The term "2-chambered right ventricle" has been applied to the division of the right ventricle into 2 chambers by aberrant, hypertrophied muscular bands.[1] HC also may result in right-sided obstruction, which is most likely a consequence of both anatomic abnormalities and dynamic factors.[7]

Our study indicates that either form of RV body obstruction can be characterized by 2-D echocardiography provided that a careful search is performed using not only the standard planes, but also several newer RV planes.[8] The optimal planes must be sought in each patient. For example, distinction can be made by 2-D echocardiography between prominences of the RV free wall and the right side of the septum. Figure 2 depicts the subcostal plane which includes the left ventricle as well as the RV outflow tract; septal anatomy can be studied in this view. As the transducer is rotated to exclude the left ventricle from view, the RV free wall appears and can be studied.

Doppler identification of disturbed RV flow is not specific for RV body obstruction, but reliable measurement of peak velocity with more advanced equipment may prove useful in computing RV pressure gradient noninvasively.

Acknowledgment: We thank Dr. Gerald F. Ryan for his help in providing case material and catheterization data.

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Quantitative Analysis of Pulmonary Vascular Disease in Simple Cardiac Anomalies With the Down Syndrome

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Intimal changes and medial thickness of small pulmonary arteries were morphometrically examined in 21 cases of simple cardiac anomalies with the Down syndrome, and their correlations with age and with pulmonary arterial peak pressure were then compared with those of 20 cases of simple cardiac anomalies without the Down syndrome and 17 cases of complete transposition of the great arteries (TGA). Results indicate that (1) intimal changes developed at an earlier age in patients with simple cardiac anomalies and the Down syndrome than in those without the Down syndrome, (2) the intimal changes were more severe than those in simple cardiac anomalies without the Down syndrome at the same level of pulmonary arterial pressure and milder than those in TGA, and (3) the media of small pulmonary arteries in simple cardiac anomalies with the Down syndrome was thinner than the media in cases without the syndrome at the same radius and the same level of pulmonary arterial pressure but thicker than the media in TGA. Retarded development of medial hypertrophy in the Down syndrome or TGA in response to pulmonary hypertension appears to make the pulmonary arteries susceptible to even moderate pressure load and appears to be responsible for early development of severe intimal changes.

Generally, pulmonary hypertension develops from infancy in cases of congenital heart disease with the Down syndrome, but the characteristics of the pulmonary vascular bed remain unclear. We previously investigated the mechanism of early development of severe pulmonary vascular disease in complete transposition of the great arteries (TGA) on the basis of morphometric assessment and hemodynamic consideration.[1] In the present study, we applied the same methods in cases of simple cardiac anomalies with the Down syndrome, and the results were compared with those obtained in cases of simple cardiac anomalies without the Down syndrome and in cases of TGA. The severity of intimal changes and medial thickness of small pulmonary arteries determined by morphometric assessment were correlated with pulmonary arterial peak pressure in each group. The results indicated that the development of pulmonary vascular disease in the Down syndrome differed from that in the group without the Down syndrome or TGA.

Methods

Patient selection: Twenty-one cases of simple cardiac anomalies with the Down syndrome including 12 cases of ventricular septal defect (VSD), 4 cases of patent ductus arteriosus (PDA), 4 cases of VSD with PDA, and 1 case of PDA with atrial septal defect (ASD) were examined in the present study. Lung specimens were obtained at biopsy in 15 cases and at autopsy in 6. The patients' ages varied from 6 months to 10 years (Table I).

Control material consisted of 20 autopsy cases of simple cardiac anomalies without the Down syndrome and 17 autopsy cases of TGA. The simple cardiac anomalies without the Down syndrome consisted of 12 cases of VSD, 2 of PDA, 2 of ASD, 3 of VSD with PDA, and 1 of ASD with PDA. Their ages ranged from 7 months to 24 years (Table II). The breakdown of TGA was as follows: 7 cases of TGA with intact ventricular septum, 9 with large VSD, and 1 with VSD and pulmonary stenosis; their ages ranged from 8 months to 12 years (Table III). Cases <6 months of age were excluded from all 3 groups of heart disease.

Cardiac catheterization was performed according to a previously reported method.[2] Pulmonary arterial pressure measured within 2 months before operation or death in all 3 groups of heart disease was taken into consideration.

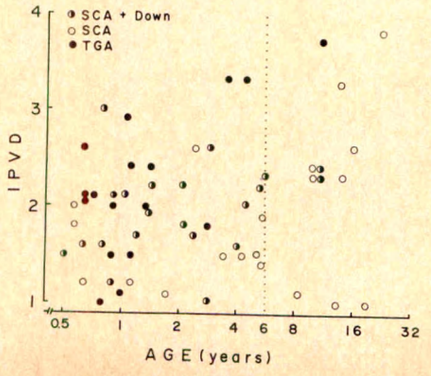

FIGURE 1. Indexes of pulmonary vascular disease (IPVD) in simple cardiac anomalies (SCA) with or without the Down syndrome and complete transposition of the great arteries (TGA) in reference to age. The **dotted vertical line** represents age 6 years.

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TABLE I Summary of Hemodynamics and Histometric Analysis in 21 Cases of Simple Cardiac Anomalies With the Down Syndrome

Case	Age	Cardiac Disease	PAP (mm Hg)	D	IPVD	D × IPVD
1	5 yr 10 mo	VSD	90/53(67)	15.2	2.2	33.4
2	10 yr	VSD	110/65(82)	17.4	2.3	40.0
3*	2 yr 1 mo	VSD	88/45(65)	12.3	2.2	27.1
4*	4 yr 11 mo	PDA	75/50(60)	12.6	2.0	25.2
5*	2 yr 6 mo	VSD	75/50(60)	12.6	1.7	21.5
6*	11 mo	VSD	75/20(35)	12.3	2.1	25.8
7*	10 mo	VSD + PDA	50/13(24)	10.4	1.6	16.6
8*	1 yr 6 mo	PDA + ASD	80/35(55)	14.1	2.2	31.0
9	3 yr 1 mo	VSD	107/53(83)	15.0	2.6	39.0
10*	10 yr 1 mo	VSD	110/60(80)	14.4	2.4	34.6
11*	4 yr	VSD	70/35(44)	11.4	1.6	18.2
12*	1 yr 3 mo	VSD + PDA	70/40(50)	11.0	1.7	18.7
13	10 mo	VSD	113/35(65)	15.5	3.0	46.5
14*	8 mo	VSD	55/20(35)	9.8	1.6	15.7
15*	6 mo	VSD	60/20(40)	10.5	1.5	15.8
16*	2 yr 3 mo	PDA	75/25(52)	10.5	1.8	18.9
17	1 yr 4 mo	PDA	55/48(52)	12.0	1.9	22.8
18*	3 yr	PDA	24/9(15)	7.9	1.0	7.9
19*	1 yr	VSD + PDA	95/30(63)	16.0	2.1	33.6
20	6 yr	VSD	120/80(100)	18.7	2.3	43.0
21*	9 mo	VSD + PDA	95/30(63)	16.0	2.1	33.6

* Biopsy case.
ASD = atrial septal defect; D = thickness of the media ($D_{R=100\ \mu m}$); IPVD = index of pulmonary vascular disease; PAP = pulmonary arterial pressure; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

TABLE II Summary of Hemodynamics and Histometric Analysis in 20 Cases of Simple Cardiac Anomalies Without the Down Syndrome

Case	Age	Cardiac Disease	PAP (mm Hg)	D	IPVD	D × IPVD
1	7 mo	VSD	120/40(64)	20.0	1.8	36.0
2	8 mo	VSD	40/10(26)	13.6	1.2	16.3
3	3 yr 7 mo	VSD	90/52(65)	14.4	1.5	21.6
4	5 yr 10 mo	VSD + PDA	90/53(67)	15.2	1.9	28.9
5	15 yr	VSD + PDA	120/64(90)	21.4	3.3	70.6
6	24 yr	VSD	128/70(90)	23.4	3.8	88.9
7	14 yr	VSD + PDA	100/48(72)	17.8	2.3	40.9
8	17 yr	VSD	110/55(85)	17.2	2.6	44.7
9	10 yr 10 mo	VSD	150/60(90)	23.8	2.4	57.1
10	1 yr 2 mo	ASD + PDA	60/22(40)	15.1	1.2	18.1
11	5 yr 6 mo	VSD	98/45(75)	17.4	1.5	26.1
12	8 yr 7 mo	VSD	28/4(12)	11.2	1.1	12.3
13	13 yr 8 mo	ASD	36/14(18)	11.2	1.0	11.2
14	18 yr 6 mo	ASD	29/9(16)	10.6	1.0	10.6
15	6 yr	PDA	75/25(47)	15.5	1.4	21.7
16	2 yr 3 mo	VSD	90/43(65)	15.1	2.6	39.3
17	10 yr	VSD	110/65(80)	17.1	2.3	40.0
18	4 yr 4 mo	VSD	46/7(23)	11.2	1.5	16.8
19	1 yr 9 mo	PDA	30/11(19)	10.3	1.1	11.3
20	7 mo	VSD	125/60(85)	19.6	2.0	39.2

Abbreviations as in Table I.

Pathologic examination: Biopsy lung tissue 1.5 by 2 by 0.5 cm obtained primarily from the lingula was fixed in 10% formalin, and a total of 30 sections from 3 blocks were made by step section at every 100 μm. In the autopsy cases, a total of 30 sections were prepared in each case from both lungs. These were stained with Goldner's trichrome combined with Weigert's stain for elastic fibers and submitted to morphometric examination.

Grading of the pulmonary vascular disease: Grading of the pulmonary arterial intimal changes was made according to the previously introduced method using an index of pulmonary vascular disease.[1–5] All pulmonary arteries encountered in our biopsy and autopsy sections were evaluated. The thickness of the media of small pulmonary arteries was assessed by a method described in our previous studies.[1,3,4,6]

Results

Pulmonary arterial changes, expressed as an index of pulmonary vascular disease, were plotted against age in all cases of simple cardiac anomalies with and without the Down syndrome and TGA (Fig. 1). There was no significant difference in the index between cases of simple cardiac anomalies with and those without the Down syndrome. However, in children <6 years of age, the index was significantly higher ($p < 0.05$) in the Down syndrome cases than in the non-Down syndrome cases (Mann-Whitney U test). Results indicate that pulmonary arterial intimal changes developed at an early stage in the Down syndrome.

TABLE III Summary of Hemodynamics and Histometric Analysis in 17 Cases of Complete Transposition of the Great Arteries

Case	Age	Cardiac Disease	PAP (mm Hg)	D	IPVD	D X IPVD
1	8 mo	TGA	70/40(55)	9.3	2.6	24.2
2	1 yr 1 mo	TGA + VSD	110/60(76)	13.3	2.9	38.6
3	3 yr 10 mo	TGA + VSD	85/40(53)	11.7	3.3	38.6
4	1 yr 6 mo	TGA + VSD	76/52(54)	10.7	2.4	25.7
5	12 yr	TGA + VSD	130/70(90)	19.7	3.7	72.9
6	1 yr 5 mo	TGA + VSD	55/33(45)	10.8	2.0	21.6
7	3 yr	TGA + VSD + PS	45/30(36)	8.6	1.8	15.5
8	11 mo	TGA	20/2(10)	8.1	1.5	12.2
9	1 yr 2 mo	TGA + VSD	100/60(80)	14.8	2.4	35.5
10	8 mo	TGA + VSD	75/30(55)	11.7	2.1	24.6
11	9 mo	TGA + VSD	80/40(57)	11.4	2.1	23.9
12	4 yr 10 mo	TGA + VSD	110/70 (85)	15.5	3.3	51.2
13	1 yr	TGA	18/7(11)	7.0	1.1	7.7
14	11 mo	TGA	48/18(34)	10.0	2.0	20.0
15	8 mo	TGA	60/40(50)	10.5	2.1	22.1
16	1 yr 2 mo	TGA	35/15(26)	9.1	1.5	13.7
17	10 mo	TGA	18/6(10)	7.5	1.0	7.5

PS = pulmonary stenosis; TGA = complete transposition of the great arteries; other abbreviations as in Table I.

A significant correlation ($p < 0.01$) was found between peak pulmonary arterial pressure and the index of pulmonary vascular disease in all 3 groups (Fig. 2). Significant differences were present in the elevation of the regression lines, whereas no differences in the slopes were found among the groups. The regression line of the Down syndrome group was slightly higher than that of the group of simple cardiac anomalies without the Down syndrome ($p < 0.05$) and significantly lower than that in cases of TGA ($p < 0.01$). In other words, the index of Down syndrome cases was higher than that in cases without the syndrome and lower than that in cases of TGA at any given level of pulmonary arterial pressure.

Consequently, it is concluded that the pulmonary arterial intimal changes in simple cardiac anomalies with the Down syndrome are more severe than those in simple cardiac anomalies without the Down syndrome even at the same pressure level and less severe than those in cases of TGA.

The pulmonary arterial peak pressure and medial thickness at a radius of 100 μm ($D_{R=100\ \mu m}$) in all cases in the 3 groups were plotted on a semilogarithmic coordinate system. The results showed significant correlation between them in all 3 groups ($p < 0.001$) (Fig. 3). In the slopes of the regression equations, there were no significant group differences. However, the elevation of the regression line in cases of simple cardiac anomalies with the Down syndrome was significantly lower than that of simple cardiac anomalies without the Down

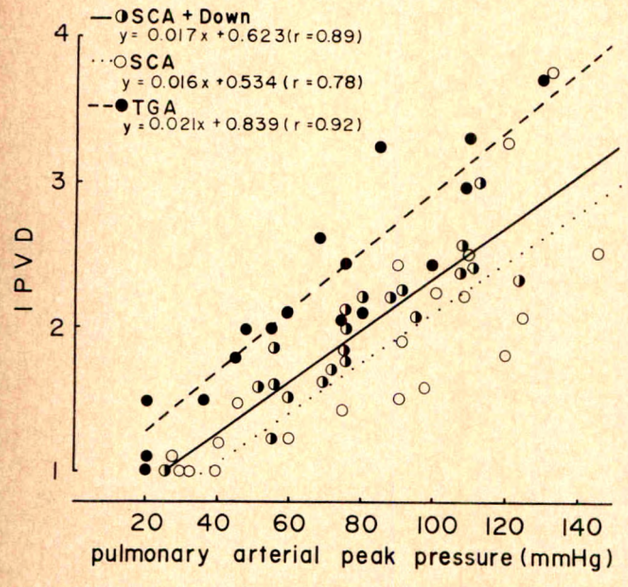

FIGURE 2. Indexes of pulmonary vascular disease (IPVD) against pulmonary arterial peak pressure in simple cardiac anomalies (SCA) with or without the Down syndrome and complete transposition of the great arteries (TGA). Correlation between the 2 parameters is observed in each group, and the regression equations obtained from the 3 groups have different elevations.

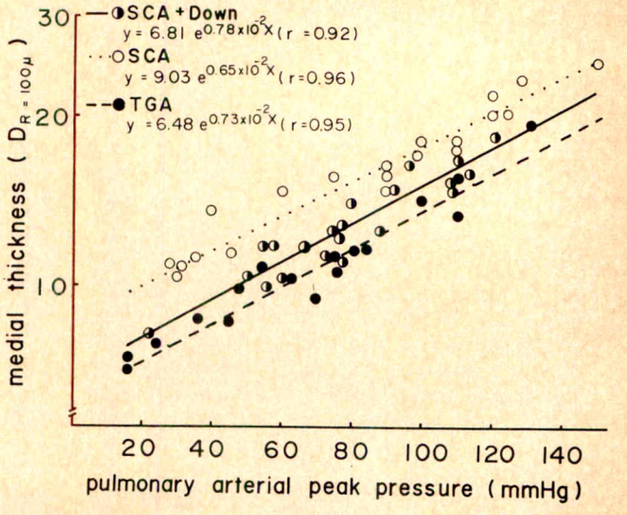

FIGURE 3. Medial thickness $D_{R=100\ \mu m}$ against pulmonary arterial peak pressure in simple cardiac anomalies (SCA) with or without the Down syndrome and complete transposition of the great arteries (TGA). Linear regressions differ among the groups. Note the difference in the elevations of regression lines among the groups.

syndrome ($p < 0.01$) and significantly higher than that of TGA ($p < 0.001$). Consequently, the media in the Down syndrome cases was thinner than that of the cases without the Down syndrome at the same level of pulmonary arterial pressure. On the other hand, it was thicker than that of TGA.

A score for the total of pulmonary vascular changes[4] was obtained by multiplying the index by the medial thickness, $D_{R=100\ \mu m}$, and the results were compared among the groups in relation to pulmonary arterial pressure on a semilogarithmic coordinate system (Fig. 4). A linear relation was found in all 3 groups, and the slopes and elevations were identical. Therefore, we conclude that the total pulmonary vascular alterations are directly proportional to the pulmonary arterial pressure and furthermore that similar scores for total pulmonary alteration are found at similar pulmonary arterial pressures, regardless of the different types of cardiac anomalies.

Discussion

Patients with congenital heart disease associated with the Down syndrome frequently develop severe pulmonary hypertension at an early age.[7–11] Park et al[12] reported severe pulmonary arterial intimal changes at an early age, but Plett et al[13] and Wilson et al[14] reported cases of TGA and complete atrioventricular canal with and without the Down syndrome and found no differences in the severity of intimal changes between the 2 groups. However, because intimal changes generally develop at an early age in cases of TGA[15] or complete atrioventricular canal[16] even without the Down syndrome, what influence the Down syndrome may have on the development of intimal changes would not be clarified in such a comparison. Therefore, the present study was undertaken to compare the intimal changes in cases with or without the Down syndrome associated with simple cardiac anomalies, in which such lesions are known to develop slowly. It could demonstrate that the index of pulmonary vascular disease in patients <6 years in age with simple cardiac anomalies associated with the Down syndrome was higher than that in patients without the syndrome. On closer investigation, there were differences among the 3 groups of simple cardiac anomalies with and without the Down syndrome and TGA with regard to the severity of intimal changes even at a certain given level of pulmonary arterial pressure. The most severe intimal changes were seen in TGA. The grade was followed by those in simple cardiac anomalies with the Down syndrome and then simple cardiac anomalies without the syndrome.

The pathogenesis of the intimal changes which are different in the Down syndrome and the non-Down syndrome must be considered. We previously investigated the mechanism of early development of pulmonary intimal changes in TGA by analyzing the response of the media of small pulmonary arteries to increasing pulmonary arterial pressure.[1] Hypertrophy of the media scarcely occurred in TGA in the first 5 months after birth even when pulmonary hypertension was present. For this reason, the media in complete transposition of the great arteries is thinner than the media in VSD in patients >6 months of age, even when similar levels of pulmonary arterial pressure are found. The present investigation using the same methods reveals that the medial thickness in simple cardiac anomalies with the Down syndrome was greater than that in TGA but less than that in simple cardiac anomalies without the Down syndrome at the same pulmonary arterial pressure level.

An increase in intraarterial pressure enhances the tension T of the arterial walls in accordance with Laplace's law: $T = (P \times R)/D$, where P is the intraarterial pressure, R the radius, and D the thickness of the media[6,17] (Fig. 5). Consequently, when P and R are constant, T is influenced by D. In the present study, the medial thickness D was found to be smallest in TGA. The order of medial thickness was followed by simple cardiac anomalies with the Down syndrome and then those without the Down syndrome under the condition that the radius and the pulmonary arterial pressure were held constant. Therefore, we can conclude that the tension of the arterial wall is greater in TGA followed, in descending order, by simple cardiac anomalies with the Down syndrome and simple cardiac anomalies without the Down syndrome. Intimal changes can occur earlier in that order. In other words, adequate medial hypertrophy in simple cardiac anomalies with pulmonary hypertension can protect the small pulmonary

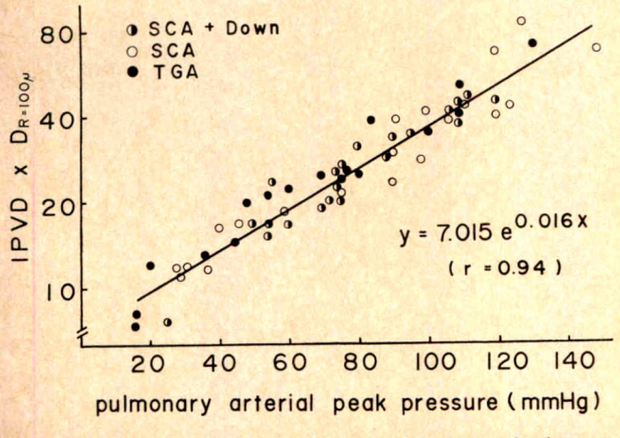

FIGURE 4. Products of medial thickness and the index of pulmonary vascular disease ($D_{R=100\ \mu m} \times$ IPVD) plotted against pulmonary arterial peak pressure in simple cardiac anomalies (SCA) with or without the Down syndrome and complete transposition of the great arteries (TGA). The 3 groups of cardiac diseases yield a common linear regression.

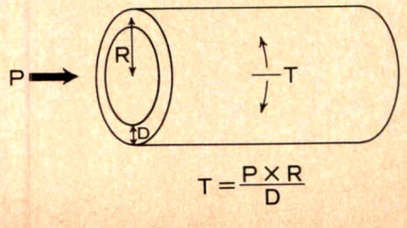

FIGURE 5. Diagram showing the relation among pressure (P), radius (R), medial thickness (D), and tension (T) in the arterial wall.

arteries from the development of intimal changes,[4] but insufficient hypertrophy of the media in cases of the Down syndrome or TGA with pulmonary hypertension fails to prevent early development of intimal changes.

Insufficient medial hypertrophy in TGA may be due to hyperoxic blood in the pulmonary circulation which is characteristic of this disease. It could suppress hypertrophy of the media.[2,18] However, in cases of simple cardiac anomalies with the Down syndrome, insufficient medial hypertrophy is unlikely to be brought about by hyperoxic blood in the pulmonary circulation. Congenital underdevelopment of the smooth muscle fibers of the media might be a probable cause.

The present study revealed different degrees of intimal changes and medial thickness of small pulmonary arteries even at a given level of pulmonary arterial pressure in 3 groups of congenital heart disease. However, the products of intimal changes and medial thickness at a given level of pulmonary arterial pressure were practically the same regardless of the type of cardiac disease, and their correlation with pulmonary arterial pressure could be represented by a regression equation common to the 3 groups of cardiac diseases. These findings suggest that the degree of pulmonary arterial pressure can be estimated histologically by the product of these 2 factors regardless of the type of cardiac disease, although these cardiac diseases have their own characteristic response of medial hypertrophy and intimal changes to increasing pulmonary arterial pressure.

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Two-Dimensional Echocardiographic Recognition Of the Right Aortic Arch

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A mirror-image right aortic arch (RAA) is frequently associated with congenital heart disease. The chest roentgenogram with or without contrast remains the noninvasive diagnostic method of choice. While 2-dimensional (2-D) echocardiography has been used to elucidate the left aortic arch (LAA), detailed description of the technique for RAA has not been reported. This study was pursued to delineate the 2-D echocardiographic approach to the patient with RAA. Twenty-seven patients in this study had LAA (Group A) and 27 had RAA (Group B). The 2-D echocardiographic examinations concentrated on the standard suprasternal long-axis (SSNL), parasternal long and short axes, and the subcostal abdominal short-axis views. When the SSNL failed to demonstrate LAA, an alternate position for RAA was utilized.

The SSNL correctly identified the LAA in all Group A patients, but in Group B it located only the ascending aorta. This simulated an interrupted aortic arch anomaly. Transducer realignment to position 2 confirmed RAA in all Group B patients. In the parasternal axes, the left descending aorta was detected posterior to the atrioventricular groove or the left ventricle in every Group A patient but in no Group B patient. The descending aorta was found to the left of the spine on the abdominal short-axis view in both groups.

The 2-D echocardiographic technique proposed for RAA is simple, rapid, and definitive. It should be pursued whenever LAA cannot be demonstrated, especially in children suspected of having a congenital heart defect. Anticipation of RAA can expedite chest and cardiovascular surgery.

A right aortic arch (RAA) is a rare cardiovascular abnormality with an incidence of 0.1%.[1] When it does occur, it is commonly associated with a congenital heart defect. It is often seen in patients with tetralogy of Fallot, double outlet right ventricle, truncus arteriosus, isolated ventricular septal defect, tricuspid atresia, and transposition of the great arteries; it is less frequently seen with other congenital heart malformations.[2]

The anteroposterior chest radiogram is the current diagnostic technique of choice. If the aortic situs is equivocal or a prominent thymus obscures proper identification, then contrast esophagography should be performed. Angiography is seldom needed and represents obvious risk, especially in a critically ill infant.

Two-dimensional (2-D) echocardiography has been used to outline a left aortic arch (LAA), coarctation and interruption of the aorta, aortic aneurysm, and double aortic arch,[3–7] but the technique for examination of the patient with RAA has not been described in detail.

This study was pursued to establish the typical findings of RAA from various scanning angles with special reference to its delineation from the suprasternal notch approach.

Methods

Two-dimensional echocardiograms were obtained in a total of 54 patients. There were 27 patients with LAA, ranging in age from 2 days to 20 years (mean 6 years) (Group A) and 27 patients with RAA with an age range of 16 months to 25 years (mean 8 years) (Group B). All had or were about to undergo diagnostic cardiac catheterization for congenital heart defects (Table I). In both groups, the definitive assessment of the aortic arch situs was determined by aortography. Prospective echocardiography was recorded in 27 consecutive Group A patients before cardiac catheterization. Because of the scarcity of RAA, only 4 patients from Group B had echocardiography before the cardiac catheterization; the other 23 were recalled for their studies.

The 2-D echocardiograms were performed in the supine patient using a Toshiba SSH-10A real-time phased array 78° sector scanner with a variable focus 2.4 MHz transducer. The 2-D echocardiograms were reviewed from a standard 3/4- or 1/2-inch videotape recorder in real-time slow motion or

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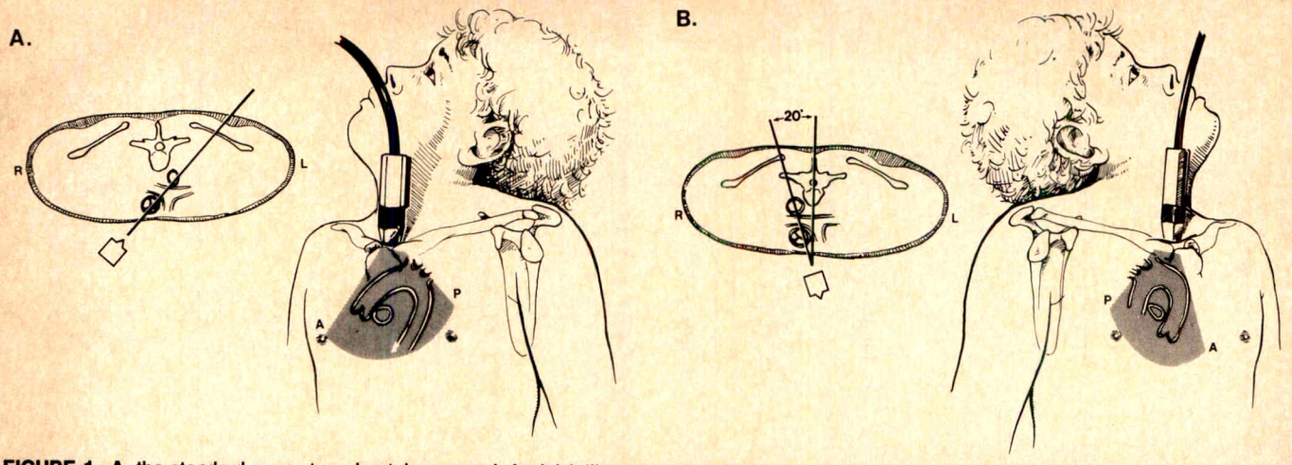


FIGURE 1. A, the standard suprasternal notch approach for LAA illustrates the sector plane extending anteriorly (A) from the right (R) nipple to the left (L) scapula posteriorly (P). The index marker of the transducer (**point**) was aimed to the back. **B,** the transducer was rotated clockwise to position 2 in search of a right aortic arch. The transducer index marker (**point**) was aimed away from the patient. The sector plane was from the left border of the sternum anteriorly to an area just to the right of the spine posteriorly. This formed an angle of approximately 20° from the midline.

frame-by-frame stop image. Photographs were made either in real-time or from a still videotape frame utilizing a Polaroid® camera. Gain settings were selected for optimal visualization of the far field in every study and then ranged from the minimum to the maximum damping positions.

All 2-D echocardiograms were obtained in 3 standard positions[8,9]: (1) standard suprasternal notch long-axis view (SSNL), (2) parasternal long-axis view, and (3) parasternal short-axis view of the left ventricle. In addition, a short-axis view of the abdomen in the subcostal position was recorded in each patient.

Special emphasis was placed upon visualization of the aorta from the suprasternal notch approach. The SSNL echocardiograms were performed with the head of the patient turned away from the midline and the neck slightly hyperextended. All SSNL studies were initiated by using position 1 (Fig. 1A). If the aortic arch could not be properly identified, then the transducer was rotated clockwise to position 2 in search of a right aortic arch (Fig. 1B). The sector plane extended from an area just to the right of the spine to the left border of the sternum. The transducer was tilted slightly toward the right and was approximately 15 to 20° from the midline.

Identification of the descending thoracic aorta was determined by noting its presence in the parasternal axes.[10] In the long-axis view, it is located posterior to the atrioventricular groove (Fig. 2A) and also posterior to the left ventricle in the short axis (Fig. 2B). The situs of the descending abdominal aorta was established from the subcostal short-axis scan of the abdomen by observing its position relative to the spine and inferior vena cava (Fig. 3).

TABLE I Findings on Diagnostic Cardiac Catheterization

Group A: LAA (n = 27)		Group B: RAA (n = 27)	
TOF	5	TOF	8
+ AVC	1	+ AVC	2
		+ COARC	1
		+ PAT	1
VSD	8	VSD	4
ASD	5	TGA complex	4
AVC	3	DORV	2
COARC	2	Ao arch anomaly	3
ASV	1	PSV	1
PSV	1	DXC	1

ASD = atrial septal defect; ASV = aortic stenosis valvar; AVC = complete atrioventricular canal; COARC = coarctation of the aorta; DORV = double outlet right ventricle; DXC = dextrocardia; PAT = pulmonary atresia; PSV = pulmonary stenosis valvar; TGA = complete transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Results

It was possible to visualize the entire aortic arch in every (100%) patient with an LAA (Group A) by using the SSNL approach (position 1). The aortic valve marked the origin of the aorta at the lower-left margin of the video scan. The brachiocephalic vessels were easily recorded in all 27 patients just before the arch turned posteriorly to form the descending aorta along the right margin of the scan (Fig. 4). The parasternal long-axis view located the descending aorta which was characterized as a pulsatile circular or oval echo-free structure posterior to the left atrium or the atrioventricular groove in every patient (Fig. 2A). Likewise, in the parasternal short-axis view, it was universally noted behind the posterior left ventricle (Fig. 2B).

When the SSNL (position 1) approach was used in the Group B patients with RAA, it was possible to visualize only the ascending aorta (Fig. 5). It failed to elucidate either the aortic arch or descending aorta in every instance. Rotation of the transducer clockwise to position 2 revealed the 3 sections of the aorta in mirror image configuration in 100% of this group. The aortic valve appeared at the lower right edge of the video scan but the brachiocephalic vessels seemed to arise more distally on the arch than in the the Group A patients. The echocardiographic course of the aorta corresponded to the expected anatomy and the aortogram in all cases (Fig. 6).

In every Group B patient, the parasternal long- and short-axes views failed to illustrate the characteristic echo-free image of the descending aorta as it had been in the Group A patients (Fig. 7). In the last 2 RAA patients who were studied, a pulsatile echo-free round

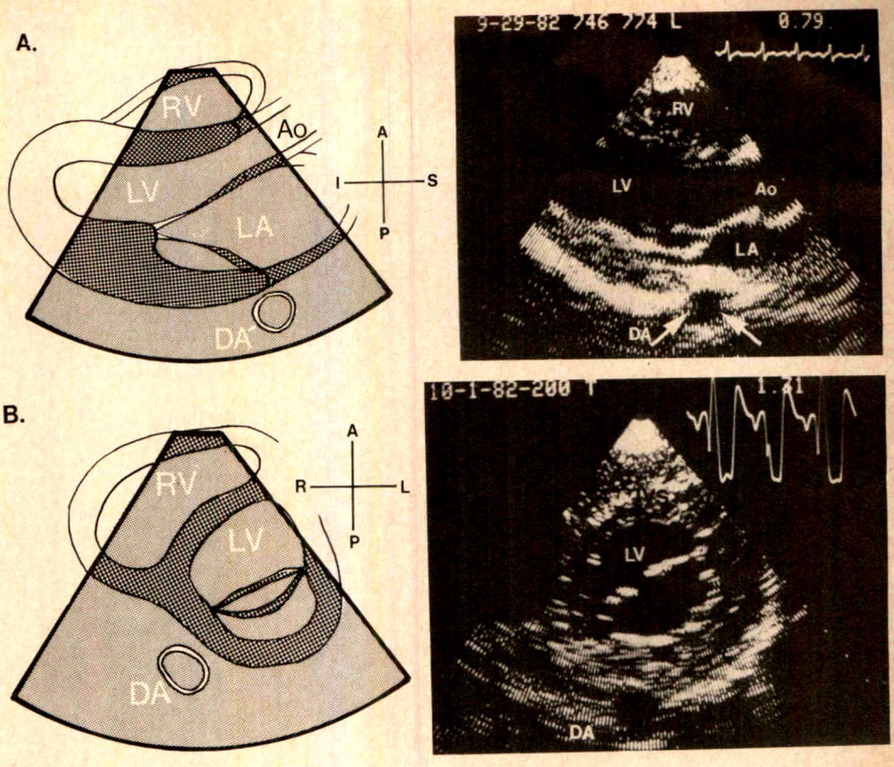


FIGURE 2. **A,** in the parasternal long-axis view, the typical left descending aorta (DA) was found behind the atrioventricular groove. **B,** the parasternal short-axis view at the level of the mitral valve classically located the left descending aorta posterior to the left ventricle (LV). Ao = aorta; LA = left atrium; RV = right ventricle; other abbreviations as before.

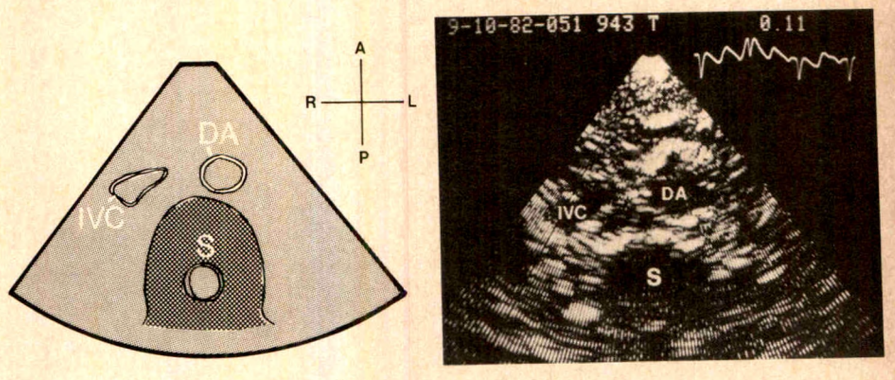


FIGURE 3. In the subcostal short-axis view of the abdomen, the descending aorta (DA) was noted as a round echo-free structure to the left of the spine (S). The inferior vena cava (IVC) was more triangular in appearance and to the right of the spine. Abbreviations as before.

structure was noted to the right of the spine in the short-axis view (Fig. 8).

The subcostal abdominal short-axis view visualized the descending abdominal aorta as a prominent pulsatile echo-free circular structure to the left of the spine in all 54 patients. The inferior vena cava, on the contrary, was always recorded to the right of the spine and appeared on the real-time image as a triangular space with venous pulsations (Fig. 3). These findings were consistent with the results of cardiac catheterization which confirmed abdominal situs solitus in every patient.

Discussion

Four major types of RAA have been described and classified.[2,11–13] They are characterized by (1) mirror-image branching of the brachiocephalic vessels, (2) an aberrant left subclavian artery, (3) an aberrant left innominate artery, and (4) isolation of the left subclavian artery from the aorta. Although RAA occurs in only 0.1% of the normal population, Stewart et al[13] reported a 98% incidence of congenital heart disease in the presence of a mirror-image RAA. Depending on the specific report, the incidence of RAA is 13 to 34% with tetralogy of Fallot, 20 to 25% with double outlet right ventricle, and 31 to 36% with truncus arteriosus.[1,2,14]

There are several situations in which identification of the situs of the aortic arch is of practical significance. Demonstration of RAA can provide indirect support when the clinician suspects associated congenital heart disease. It alerts the cardiologist that the infant with a ventricular septal defect might be at greater risk of developing a tetralogy-like physiology. Furthermore, the 2-D echocardiographic technique can be used to

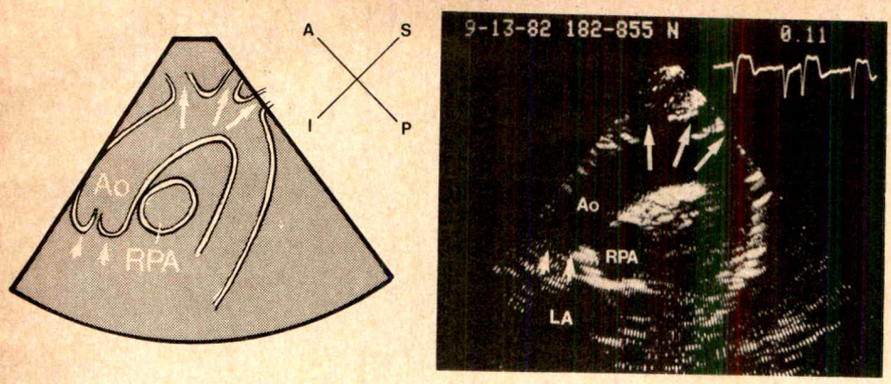
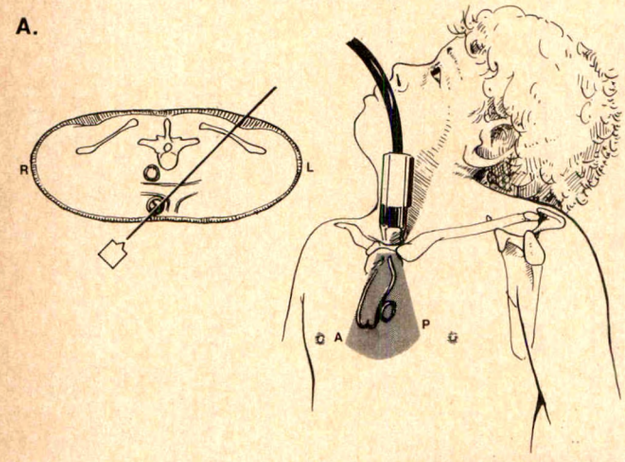


FIGURE 4. The typical left aortic arch was characterized by movement of the aortic valve leaflets (**short arrows**) at the lower-left margin of the scan followed by the brachiocephalic vessels (**long arrows**) and the descending aorta. RPA = right pulmonary artery; other abbreviations as before.



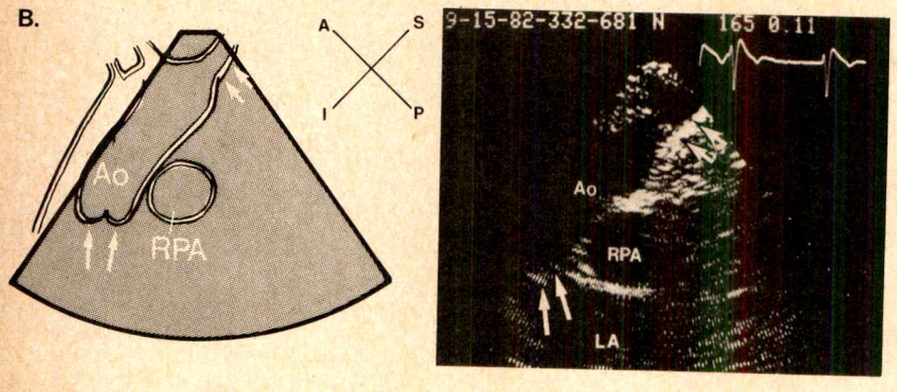


FIGURE 5. A, this illustration depicts why the standard suprasternal notch approach transects only part of the aorta in patients with RAA. **B,** only the ascending aorta was clearly visualized above the aortic valve (**long arrows**) when position 1 was pursued in this patient with RAA. It simulated an interrupted aortic arch anomaly (**short arrows**). Abbreviations as before.

confirm the presence of RAA in the tetralogy of Fallot patient awaiting a Blalock-Taussig shunt. A higher incidence of patency results when these anastomotic procedures are performed on the side opposite to the descending aorta.[15] Anticipation of the correct anatomy helps to avoid a less advantageous shunt. The infant with a tracheo-esophageal fistula represents another instance in which awareness of RAA is important. Chest surgeons prefer to approach such repairs without encountering the aorta. To expedite surgery, they use a thoracotomy contralateral to the descending aorta. If there is any question concerning the exact situs of the aortic arch from the chest roentgenogram, it can be easily resolved by the 2-D echocardiographic technique before cardiac catheterization or surgery.

Snider and Silverman,[5] in a large series detailing the standard suprasternal notch approach, were able to correctly identify RAA in 76% of their cases. However, they did not elaborate on the study technique for RAA. Although our study was somewhat retrospective, we encountered no difficulty in clearly locating the RAA. This was especially true when a systematic search was followed in all 3 scanning views. Under these conditions the correct situs of the aortic arch was easily detected in every patient. Lastly, it must be emphasized that the sector plane in search for RAA is usually only 15 to 20°

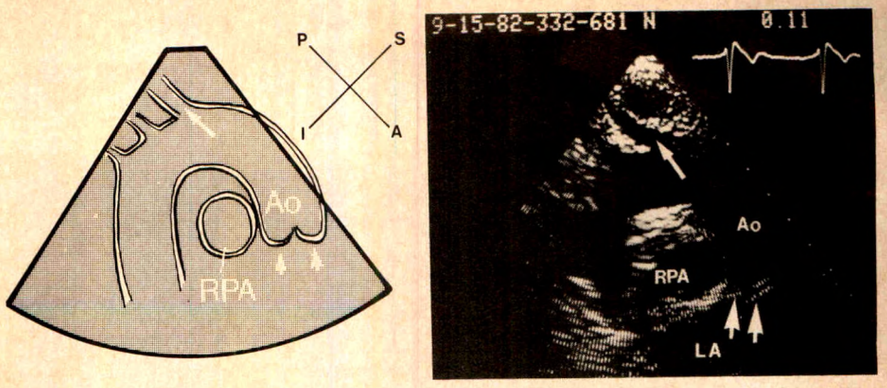


FIGURE 6. Clockwise rotation of the transducer to position 2 in patients with RAA revealed the arch corresponding to its anatomic configuration. The aortic valve (**short arrows**) was located at the lower right border of the scan and the brachiocephalic vessels (**long arrows**) pointed toward the side of the descending aorta. Abbreviations as before.

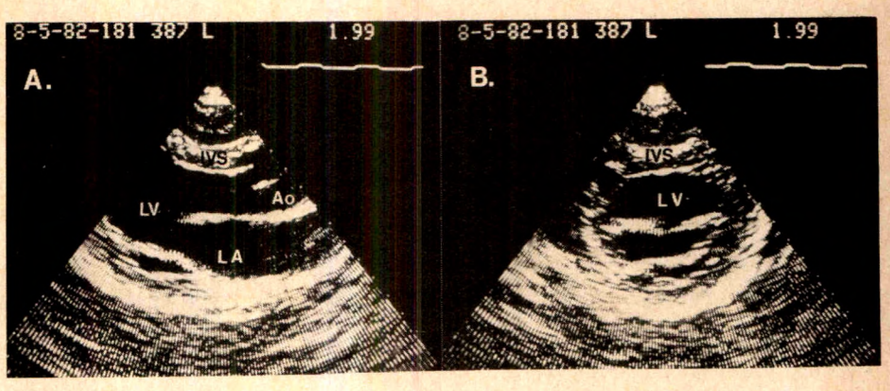


FIGURE 7. The parasternal long-axis (**A**) and short-axis (**B**) views in this patient with RAA failed to demonstrate the typical echo-free structure of the descending aorta in the far field. Abbreviations as before.

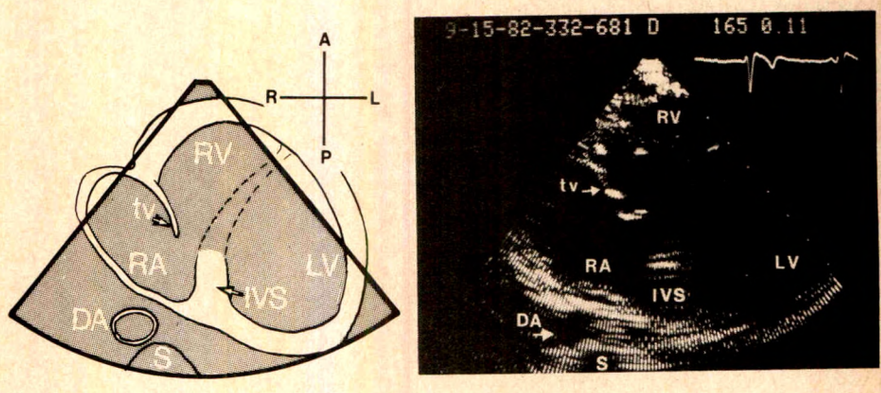


FIGURE 8. An echo-free pulsatile structure believed to be a right descending aorta (DA) was discovered on the parasternal short axis to the right of the spine (S) behind the right atrium (RA) in this Group B patient. tv = tricuspid valve; other abbreviations as before.

from the midline (Fig. 1B). This differs from the 45° angle that is commonly used with the standard suprasternal notch approach to identify LAA.[4]

The SSNL approach may be more tedious in uncooperative, unsedated, or severely ill pediatric patients. In these cases, the parasternal views exclude the possibility of RAA when the typical pulsatile circular or oval echo-free descending aorta is visualized posteriorly in the atrioventricular groove or behind the left ventricle. The 4 major types of RAA all remain to the right of the spine before crossing to the left a short distance above the diaphragm.

A round pulsatile echo-free structure resembling the usual cross-sectional aortic image was discovered on the parasternal short-axis view behind the right atrium in the last 2 patients with RAA. We believed it to be the right descending aorta. This would provide a positive diagnostic sign of RAA rather than a diagnosis of exclusion as described in the preceding paragraph. Unfortunately, we did not have the opportunity to confirm it by contrast studies. Additional study of the parasternal and 4-chamber views to outline the descending aorta should further define its course.

When the SSNL approach was used in the RAA patients, only the ascending aorta could be visualized. Failure to demonstrate the arch or descending aorta simulated an interruption of the aorta at the level of the arch (Fig. 5). This pattern may on occasion be confused

with other anomalies of the aortic arch including interruption, hypoplasia of the isthmus, or severe coarctation of the aorta. It is, therefore, advisable to thoroughly search for an RAA whenever this pattern is confronted.

We chose to rotate the transducer clockwise from the standard suprasternal notch approach in search of RAA because the resulting image corresponded to the anatomy and angiography of an arch looping to the right of the patient. Counterclockwise rotation[5] or turning the transducer indicator toward the patient produced a video image with the arch looping toward the left. Without labeling or indication of the transducer location, the counterclockwise technique displays an image indistinguishable from a true LAA.

The 2-D echocardiographic technique for recognition of RAA, as outlined, is simple, rapid, and definitive. The approach should be incorporated into the standard echocardiographic examination especially when LAA cannot be determined from the plain chest roentgenogram. Furthermore, it should be pursued in any child suspected of having a congenital heart defect where there is a strong association with RAA. Lastly, anticipation of an RAA can be used to expedite chest as well as cardiovascular surgery.

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SYMPOSIUM ON RESULTS OF THE MUSTARD OPERATION FOR COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

JAMES R. ZUBERBUHLER, MD, GUEST EDITOR

Introduction

JAMES R. ZUBERBUHLER, MD

Transposition of the great arteries (TGA) is an important congenital cardiac anomaly that regularly produces severe and life-threatening symptoms early in life. Before treatment was available, the outlook for survival was grim indeed, and although the introduction of surgical atrial septectomy provided a means of improving interatrial mixing, the mortality associated with this procedure was high. The development of balloon atrial septostomy by Rashkind and Miller[1] and of an intraatrial baffle repair technique by Mustard[2] in the mid-1960s resulted in a dramatic change in prognosis. The widespread use of balloon septostomy markedly decreased the early morbidity and mortality in TGA so that most patients survived early infancy.

One early attempt at surgically correcting the abnormal hemodynamics of TGA was directed at what seemed to be the central difficulty, the abnormal origin of the aorta and pulmonary artery.[3] Soon after, Baffes[4] pioneered the "venous" approach to the problem and Senning[5] devised still another "venous" operation, but the results of these procedures were not encouraging. Therefore, the apparently successful Mustard technique achieved widespread popularity shortly after the first report appeared in 1964. Further improvement in early morbidity and mortality was subsequently achieved by the Park blade septostomy technique[6] and by application of the Mustard operation to younger infants, in some institutions even during the first few weeks of life.

Problems remain, however, especially in patients with associated cardiac abnormalities. The presence of a large interventricular communication complicates the management of TGA, and whether an early intraatrial baffle repair with surgical closure of the ventricular septal defect is superior to early banding of the pulmonary trunk and a subsequent intracardiac procedure remains controversial. Pulmonary stenosis is also a difficult problem, especially because most obstruction is subvalvular. The left ventricular outflow tract is a thorny surgical path, because the anterior leaflet of the mitral valve is an integral part of this area and there is no true infundibulum to be "cored out." Conduits have been used to bypass the obstruction, but they have inherent limitations and hazards.

Long-term results are less well defined than are operative risk and short-term survival. There is concern over dysrhythmias, over the capacity of the tricuspid valve and its support apparatus to tolerate systemic pressures for many years, and over the continued integrity of the right ventricular myocardium, "designed" to pump at much lower than systemic pressure. The course of pulmonary stenosis, especially in patients with an intact ventricular septum, is another nagging worry.

In addition to concern about long-term survival of patients who have intraatrial repair, there is also apprehension about their functional capacity. Will it be possible for these individuals to hold down a job, to bear children, and to participate in recreational sports? These questions have become more pressing as alternative surgical techniques have appeared on the scene.[7,8] Is it justifiable to accept the higher surgical mortality of an "arterial switch" operation because of better long-term results? First, we must know the long-term results of intraatrial baffle operations so that we may have a standard against which other operative techniques may be judged.

This investigation was undertaken to address the question of long-term results. Admittedly, "long-term" is not really very long, but it is the best we have. Other studies have focused on specific measures of success or failure, such as postoperative hemodynamics, the incidence and nature of electrical abnormalities, and the results of exercise testing. To our knowledge, no comprehensive study of overall results in a group of patients from a single institution has been published, and the present study was carried out in the hope that several views of one "elephant" are more likely to describe accurately than are several views of as many "elephants."

From 1964 through 1980, 95 patients survived more than 1 month after a Mustard procedure performed at the Children's Hospital of Pittsburgh, and these patients form the basis of this study. Of the 95 survivors, 82 had both pre- and postoperative cardiac catheter-

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ization; most had more than 1 preoperative study and several had serial postoperative catheterizations. The hemodynamic and cineangiographic findings are described in the first paper. Almost all patients had multiple electrocardiograms, and most had other electrical investigation such as intracardiac electrophysiologic studies in 60 patients and 24-hour electrocardiographic monitoring in 21. The results of the review of the electrocardiographic and electrophysiologic studies are reported in the second paper. The exercise and radionuclide evaluations were performed in a smaller subset of about 50 survivors who are now more than 7 years of age. Roughly 20 patients participated in each of these studies, not necessarily the same individuals in each group. The patients were selected only by distance from Pittsburgh and by willingness of the individuals and their parents to participate. A psychological evaluation of older survivors (to be published elsewhere) documented strong death fears in both patients and their parents and also an inability of patients to deal with their body image. It also showed a striking dearth of communication skills; patients found it very difficult to talk with friends or parents about the fears and concerns centered about their cardiac problem.

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Hemodynamic Function After the Mustard Operation for Transposition of the Great Arteries

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Pre- and postoperative cardiac catheterization data and cinenangiocardiograms of 82 patients who survived the Mustard operation for transposition of the great arteries (TGA) were reviewed. The postoperative catheterizations were performed 20 days to 10 years after operation (mean 2.5 years). Forty-six patients (56%) had no or insignificant associated cardiac lesions, whereas 36 (44%) had ventricular septal defect, pulmonary stenosis, or both, and required surgical intervention at the time of the Mustard operation. Postoperatively, 11 patients (13%) had significant systemic venous obstruction. Of the 11 patients, 6 required reoperation, and 2 patients had evidence of restenosis or complete obstruction in the superior vena cava after reoperation. In most patients, superior vena caval obstruction was well tolerated even in the presence of high pressure in the superior vena cava. Pulmonary venous obstruction occurred in 5 patients (6%), 3 of whom had no clinical symptoms despite severe pulmonary venous obstruction, although all had radiographic evidence of pulmonary venous congestion. The incidence of obstruction was drastically reduced after the Mustard operation was modified to include routine enlargement of the pulmonary venous atrium. Tricuspid regurgitation was uncommon (10%), but did occur in patients who had transatrial closure of a ventricular septal defect. Preoperatively, left ventricular outflow obstruction occurred in 38%. In 12 patients an attempt was made to relieve the obstruction at surgery. The 6 patients who had localized obstruction had a good result, but patients with more diffuse narrowing of left ventricular outflow had little or no relief of obstruction. Mild to moderate left ventricular outflow gradients regressed spontaneously in most patients after the Mustard operation.

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The introduction of both the Mustard operative technique[1] and Rashkind balloon atrial septostomy[2] in the mid-1960s resulted in a dramatic change in the management and prognosis of patients with transposition of the great arteries (TGA). Although in recent years various surgical techniques have been employed, the Mustard operation remains the most commonly used in physiologic correction of this cardiac lesion. Several previous reports described operative complications and short- and long-term hemodynamic problems after the Mustard operation.[3–10] Complex electrophysiologic disturbances[11–14] and abnormalities of ventricular function[15–17] have also been recognized. This study focuses on hemodynamic abnormalities documented by serial cardiac catheterization studies performed before and after operation. An attempt was made to determine if a correlation exists between specific postoperative hemodynamic abnormalities and preexisting associated cardiac malformations or operative techniques.

Methods

From 1964 to 1980, there were 95 long-term survivors of the Mustard operation for TGA at Children's Hospital of Pittsburgh. The study group consists of 82 of the 95 survivors, and all 82 had both pre- and postoperative cardiac catheterization and angiocardiography.

Associated cardiac lesions: Forty-six patients (56%) had either no associated intracardiac anomaly (34 patients) or only a tiny ventricular septal defect (4 patients), patent ductus arteriosus (2 patients) or aortic coarctation (1 patient). The remaining 36 patients had a significant intracardiac malformation such as a ventricular septal defect (24 patients), pulmonary stenosis (6 patients), or both (6 patients) and the defect was repaired at the time of the Mustard operation.

Operative technique: Before the Mustard operation, 30 patients had had 31 palliative surgical procedures: 20 patients a Blalock-Hanlon atrial septectomy, 7 a banding of the pulmonary trunk, and 4 a Blalock-Taussig shunt. At the time of the Mustard operation, age ranged from 0.3 to 13.7 years (mean 3.2) and weight from 4.9 to 37 kg (mean 12.3). In 18 patients intracardiac operations were performed using the standard normothermic cardiopulmonary bypass. Moderate systemic hypothermia (28°C) and cardiopulmonary bypass were used in 34 patients and deep hypothermia (18°C) and total circulatory arrest in 30. In 74 patients (90%) autogenous parietal pericardium was used to construct the baffle, whereas in the remaining 8 patients various materials were used: Dacron® in 4, bovine pericardium in 3, and Gore-Tex® in 1. The pulmonary venous atrium was enlarged in 39 patients, using Gore-Tex (30 patients), autogenous pericardium (6 patients), or bovine parietal pericardium (3 patients). Early in the series the coronary sinus was incised to permit coronary sinus blood drainage into the systemic venous atrium, but during the past 10 years the coronary sinus was left intact and the suture line was placed so that the coronary sinus blood drained into the pulmonary venous atrium.

Cardiac catheterization: Each patient had at least 1 preoperative and 1 postoperative cardiac catheterization. Sixty-seven (82%) had balloon atrial septostomy at the time of the first catheterization. Six patients had blade atrial septostomy at 1 to 5 months of age because of an inadequate interatrial opening after an initial balloon septostomy in the newborn period. All but 4 of the 82 patients had a second or third cardiac catheterization before the Mustard operation. The first postoperative cardiac catheterization was performed 20 days to 10 years after operation (mean 30 months). Twelve patients had a second postoperative catheterization and 2 had a third study.

Either a percutaneous or a cutdown technique was used, usually from an inguinal approach. An antecubital or axillary cutdown was performed when femoral or iliac venous thrombosis precluded a femoral approach (12 patients) or when a catheter could not be advanced into the superior vena cava from the systemic venous atrium because of severe baffle obstruction (3 patients).

No premedication was given to infants <6 months of age and morphine sulfate (0.1 mg/kg) was used in infants 6 to 12 months of age. For older children, a combination of meperidine (2 mg/kg), chlorpromazine (0.5 mg/kg), and promethazine (0.5 mg/kg) was used. In postoperative studies, the usual hemodynamic data were supplemented by withdrawal pressures from both the superior and inferior vena cava to the systemic venous atrium to identify systemic venous obstruction. Also, simultaneous pressure recordings were made in the right ventricle and in either the pulmonary arterial wedge position or the proximal pulmonary venous atrium or pulmonary vein to rule out pulmonary venous obstruction. The pulmonary venous atrium was entered by a catheter passed retrograde through the aortic and tricuspid valves or, in a few patients, from the systemic venous atrium through a baffle defect. Biplane cineangiograms routinely included injections of contrast medium into the right and left ventricles and the superior and inferior venae cavae. Other selective injections were performed as needed to define suspected anatomic abnormalities.

Statistics: All numerical data in this report are expressed as mean ± 1 standard deviation. Statistical analysis was performed using Student's *t* test.

Results

Baffle dysfunction was diagnosed when an interatrial communication could be demonstrated by catheter passage, oximetry, or cineangiography, or when there was cineangiographic or pressure recording evidence of systemic or pulmonary venous obstruction.

Baffle leakage: A baffle leak was noted in 22 patients (25%). Of the 4 patients with oximetric evidence of shunting, 1 had a large left-to-right shunt (Qp/Qs = 1.8:1) and another had a right-to-left shunt large enough to cause the systemic arterial saturation to decrease <90%. Both patients required reoperation. Two others had small shunts (Qp/Qs <1.2:1) detected by oximetry and did not require reoperation. In 18 (82%), trivial leakage was noted by cineangiography but not by oximetry.

Systemic venous obstruction: In the 78 patients in whom pressure in both the superior vena cava and systemic venous atrium could be measured, the mean gradient was >5 mm Hg in 22. Patients with a gradient <10 mm Hg had no clinical evidence of systemic venous obstruction, except for 1 patient who had transient facial edema in the early postoperative period. In 11 patients the gradient was between 10 and 18 mm Hg (Table I). Of these, 4 had clinical manifestations of superior vena caval obstruction, such as facial edema or a prominent venous pattern on the chest wall, but the remaining 7 had no signs or symptoms, even though obstruction was complete in 2 patients. In these latter patients superior vena caval obstruction was an incidental finding at cardiac catheterization. Simultaneous or near simultaneous pressure in the systemic venous

TABLE I Severe Systemic Venous Obstruction

Pt	Age (mo) at Op	Wt (kg) at Op	Baffle Material	Interval to Postop Cath (mo)	Pressure (mm Hg) SVC	SVA	IVC	ΔSVC-SVA	ΔIVC-SVA	Course
Operated Patients										
1*	12	7.8	Bovine	3	20	NE	NE	. . .	. . .	SVO after reop, 2nd reop done
2*	24	10.4	P	13	22	5	5	17	0	Well after reop
3*	19	9.0	P	3	20	6	NE	14	. . .	Died early postoperatively
4†	22	9.0	P	22	20	4	6	16	2	Relief of SVO and PVO after reop
5*	49	13.0	Dacron	29	20	2	10	18	8	Complete SVO after reop
6	22	10.0	P	20	26	10	10	16	0	Relief after reop
Unoperated Patients										
1	66	15.0	P	103	16	5	5	11	0	Well 15 yr postoperatively
2	2	4.9	P	15	15	3	3	12	0	Well 1 yr postoperatively
3	16	8.0	P	3	15	5	7	10	2	Well 4 yr postoperatively
4	28	9.4	P	9	24	6	6	18	0	Well 3 yr postoperatively
5	61	14.0	P	9	23	7	8	17	1	Well 3 yr postoperatively

* Clinical signs of systemic venous obstruction.
† Also had pulmonary venous obstruction.
Cath = cardiac catheterization; IVC = inferior vena cava; NE = not entered; op = operation; P = pericardium; postop = postoperative; PVO = pulmonary venous obstruction; reop = reoperation; SVA = systemic venous atrium; SVC = superior vena cava; SVO = systemic venous obstruction; wt = weight; Δ = gradient.

TABLE II Pulmonary Venous Obstruction

Pt	Age (mo) at Op	Weight (kg) at Op	Interval to Postop Cath (mo)	PA Wedge or Prox PVA (mm Hg)	Distal PVA (mm Hg)	Gradient (mm Hg)	Course
1*	16	7.5	4	40	3	37	Died intraoperatively
2*	34	11.5	17	40	5	35	Relief of gradient
3	40	15.0	14	24	2	22	Relief of gradient
4	22	9.0	22	22	6	16	Relief of gradient
5	22	10.0	14	26	3	23	Clinically well

* Symptomatic.
All patients had pericardium for baffle.
PA = pulmonary artery; prox = proximal; PVA = pulmonary venous atrium; other abbreviations as in Table I.

TABLE III Systemic and Pulmonary Venous Obstruction After the Mustard Operation

Group	SVO (n = 6*)	PVO (n = 5*)	Entire Group (n = 82)
Age at op (yr)	1–4.2 (Mean 2.1)	1.3–3.3 (Mean 2.2)	0.3–13.7 (Mean 3.2)
Weight at op (kg)	7.8–13.0 (Mean 9.9)	7.5–17.0 (Mean 10.6)	4.9–37.0 (Mean 12.3)
Baffle material	4 Percardium 1 Dacron 1 Bovine	5 Pericardium	74 Pericardium 4 Dacron 3 Bovine 1 Gore-Tex
PVA enlarged	2 No 4 Yes	4 No 1 Yes	43 No 39 Yes

* One patient had systemic and pulmonary venous obstruction.
Abbreviation as in Tables I and II.

atrium and both venae cavae was not obtained in 13 patients (4 in the superior and 9 in the inferior vena cava). Eleven had no cineangiographic evidence of venous obstruction.

Four symptomatic patients and 2 with severe systemic venous obstruction without signs or symptoms underwent reoperation to relieve obstruction 3 months to 3 years after the initial Mustard operation (mean 16 months). One patient required operation for severe venous obstruction between the systemic venous atrium and both the superior and inferior venae cavae. No patient had isolated inferior vena caval obstruction. One of the 6 patients reoperated on for systemic venous obstruction died. The 5 survivors had repeat cardiac catheterization after reoperation. Three were improved but 2 had severe residual caval obstruction. One had complete obstruction of the superior vena cava but good collateral venous connections to the inferior vena cava through the azygos system. The other patient continued to have severe symptoms of superior vena caval obstruction but improved after a second surgical attempt to relieve the obstruction. Five patients with severe superior vena caval obstruction and gradients ranging from 10 to 18 mm Hg had adequate collateral venous drainage through the azygos or hemiazygos vein and have not undergone reoperation.

Pulmonary venous obstruction: When pulmonary arterial wedge pressure or pulmonary arterial diastolic pressure was >10 mm Hg, simultaneous pulmonary arterial wedge and right ventricular end-diastolic pressures were recorded. In some patients a retrograde catheter was passed across the tricuspid valve into the

proximal pulmonary venous atrium, and pressure was recorded there and on withdrawal to the distal pulmonary venous atrium to document the presence and severity of pulmonary venous obstruction. The pressure gradient was >10 mm Hg in 5 patients and ranged from 16 to 37 mm Hg (Table II). In 2 of these 5 patients symptoms of pulmonary venous obstruction developed 2 to 12 months after operation. Although each of the 5 had radiographic evidence of pulmonary venous obstruction, 3 patients had no symptoms. Reoperation was performed in all 5 patients 4 to 24 months (mean 6) after the initial Mustard operation. One patient also had repair of superior vena caval obstruction. There was 1 intraoperative death. The remaining 4 patients had repeat cardiac catheterization 13 to 24 months after reoperation and relief of pulmonary venous obstruction was documented in all.

Overall, reoperation for systemic or pulmonary venous obstruction, or both, was required in 10 patients. Their age and weight at the initial operation were slightly lower than those of the entire group, but the differences were not statistically significant (Table III). Because pericardium was used for the original baffle in most patients, the role of this material in the occurrence of venous obstruction cannot be assessed. Pulmonary venous obstruction was uncommon in the entire group, but was significantly more common among patients who did not have surgical enlargement of the pulmonary venous atrium.

Ventricular septal defect: In 39 (48%) of 82 patients a ventricular septal defect was demonstrated at the initial preoperative catheterization. The defect closed spontaneously in 11 (28%) and 4 had a very small defect that required no surgical intervention. The remaining 24 patients had surgical closure of the defect at the time of the Mustard operation. In 15 the defect was small and required only suture closure, whereas 9 had patch closure of a large defect. In 21 patients (88%) the defect was closed from a transatrial approach, whereas in the remaining 3 the defect was closed using a transpulmonary approach (2 patients) or by ventriculotomy (1 patient). Seven patients also required removal of a previously placed pulmonary artery band. Of the 24 patients who had surgical closure of a ventricular septal defect, 5 had a residual defect at postoperative cardiac catheterization. However, in only 1 patient was there a large enough left-to-right shunt (Qp/Qs >2:1) to require reoperation.

Tricuspid regurgitation: This was seen in 6 (25%) of 24 patients who had surgical closure of a ventricular septal defect. In 4 of these patients it was mild, but in 2 it was severe enough to require reoperation. One of the 2 had replacement of the tricuspid valve with a Hancock prosthesis and the other had repair of torn chordae. Three patients with tricuspid regurgitation had grossly abnormal right ventricular function on cineangiography. Mild tricuspid regurgitation and angiocardiographic evidence of right ventricular dysfunction were seen in 2 additional patients who did not have surgical closure of a ventricular septal defect (3%). Apparently, significant tricuspid regurgitation and severe right ventricular dysfunction were most commonly related to surgical closure of a ventricular septal defect through the tricuspid valve.

Pulmonary stenosis: Of 42 patients who had cardiac catheterization during the first week of life, 17 had measurement of pulmonary arterial pressure. None had a left ventricular outflow gradient >20 mm Hg, even though some had documented pulmonary stenosis at a subsequent catheterization. Data from serial preoperative cardiac catheterizations demonstrated that a gradient usually became evident during the first few months of life and then tended to increase with age (Fig. 1). Thirty-one patients were found to have pulmonary stenosis, defined as a pressure gradient between the left ventricle and the pulmonary artery >20 mm Hg at preoperative cardiac catheterization. Twelve of these 31 patients had attempted surgical repair of the obstruction. Six of the 12 had localized obstruction, consisting of pulmonary valve stenosis in 3, an aneurysm of the ventricular septum in 2, and a discrete membrane in 1. Each had substantial reduction of the gradient after operation (mean preoperative gradient 61 ± 5 mm Hg, mean postoperative gradient 32 ± 16 mm Hg, p <0.001) (Fig. 2). Another 6 patients had more diffuse left ventricular outflow obstruction and surgical results were poor, with no significant reduction in gradient (preoperative gradient 62 ± 17 mm Hg, postoperative gradient 55 ± 18 mm Hg, p not significant) (Fig. 2).

In the remaining 19 patients no attempt was made to relieve the pulmonary stenosis. In 9 the left ventricular outflow tract and pulmonary valve were inspected at surgery and no significant abnormalities were found. Most of the 19 patients had spontaneous regression of the pressure gradient after the Mustard operation

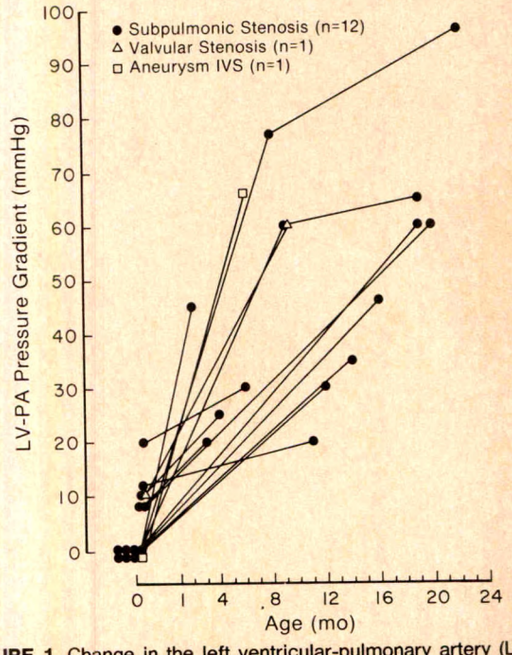

FIGURE 1. Change in the left ventricular-pulmonary artery (LV-PA) pressure gradient before the Mustard operation in patients <1 month of age when the gradient was measured. IVS = interventricular septum.

(mean preoperative gradient 32 ± 12 mm Hg, mean postoperative gradient 18 ± 14 mm Hg, p <0.001) (Fig. 3).

In summary, most (56%) patients had some degree of hemodynamic abnormality after the Mustard operation (Table IV), but only 15 patients (18%) have required reoperation. There were 3 surgical deaths in patients requiring repeat operation and the remaining patients have been clinically well despite the presence of minor hemodynamic abnormalities.

Discussion

With increasing experience with the Mustard operation, significant postoperative hemodynamic problems have become less common. Controversy as to the optimal baffle material and surgical technique persists.[18–20] Because surgical morbidity and mortality vary among institutions, it is difficult to substantiate the superiority of one surgical technique or a specific baffle material over another.

A hemodynamic abnormality related to baffle dysfunction was the most common problem demonstrated in this study. The severity of obstruction as judged by the gradient between the superior vena cava and the systemic venous atrium does not always correlate well with clinical symptoms. All patients with clinical evidence of superior vena caval obstruction had a pressure gradient ≥14 mm Hg between the superior vena cava and the systemic venous atrium, but 4 other patients with even higher gradients had no clinical signs of superior vena caval obstruction. The severity of symptoms is clearly related to the adequacy of collateral venous drainage. All asymptomatic patients with severe or complete superior vena caval obstruction were shown to have collateral venous drainage through the azygos or hemiazygos system, or both. Despite the absence of signs and symptoms of severe caval obstruction and the presence of collateral channels, superior vena caval pressure ranged from 15 to 24 mm Hg. Most symptomatic patients also had collateral channels on angiographic study. Therefore, neither the level of pressure in the superior vena cava nor the status of collateral vessels seems to be the sole determinant of clinical symptoms. Some patients with high superior vena caval pressure and severe obstruction are doing well ≥15 years postoperatively. In others, the gradient may actually decrease. One patient had moderate superior vena caval obstruction (gradient 8 mm Hg) documented at a 3-month postoperative cardiac catheterization, but repeat study 3 years after operation showed spontaneous regression of the gradient to only 2 mm Hg. The importance of the azygos vein as a major collateral

TABLE IV Overall Incidence of Hemodynamic Abnormalites and Reoperation After the Mustard Operation (n = 82)

Abnormalities	Frequency n	Frequency %	Reop	Mortality
SVO	17	21	5	1
PVO	6	7	4	1
SVO and PVO	1	1	1	0
Baffle leakage	4	5	2	1
Residual VSD	5	6	1	0
Tricuspid regurgitation	8	10	2	0
Right ventricular dysfunction	5	6	. . .	. . .
Total			15	3

RV = right ventricle; VSD = ventricular septal defect; other abbreviations as in Table I.

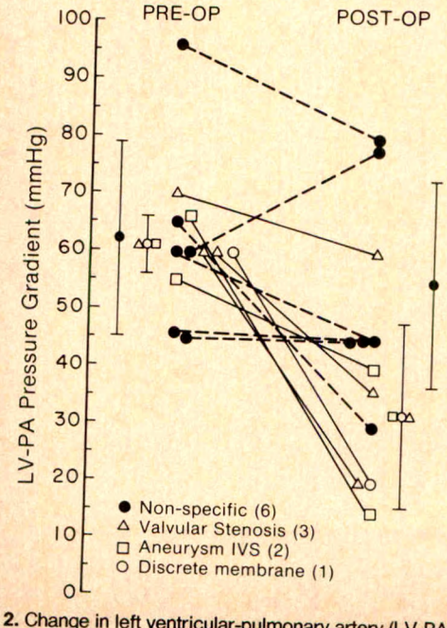

FIGURE 2. Change in left ventricular-pulmonary artery (LV-PA) pressure gradient after the Mustard operation and surgical repair of left ventricular outflow obstruction in 12 patients. IVS = interventricular septum; post-op = postoperative; pre-op = preoperative.

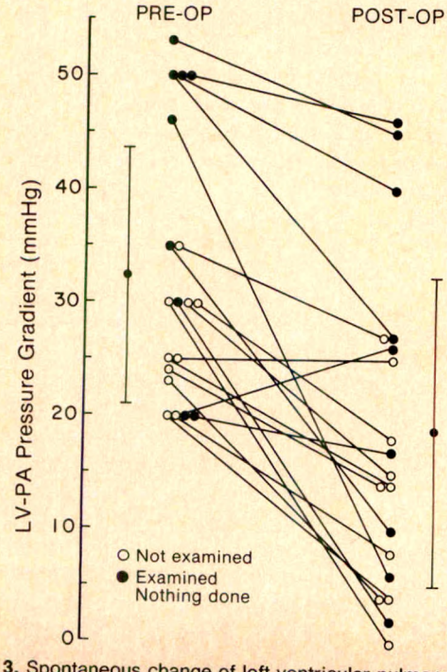

FIGURE 3. Spontaneous change of left ventricular-pulmonary artery (LV-PA) pressure gradient after the Mustard operation in 19 patients in whom pulmonary stenosis was not repaired. Abbreviations as in Figure 2.

channel makes it desirable to preserve the azygos venous system at the time of the Mustard operation if at all possible. Venous obstruction at the junction of the inferior vena cava and right atrium is rare and was seen in only 1 patient. The combination of superior and inferior vena caval obstruction is poorly tolerated but fortunately is rare.

Pulmonary venous obstruction is relatively uncommon. The frequency was even further reduced after routine enlargement of the pulmonary venous atrium was introduced at the time of the Mustard operation. In contrast to superior vena caval obstruction, there are no collateral channels in this type of venous obstruction. Consequently, pulmonary venous congestion and pulmonary hypertension are inevitable when the obstruction is severe. Stark et al[4] reported that pulmonary venous obstruction is poorly tolerated and may cause sudden death. However, 3 of 5 patients had no symptoms despite severe pulmonary venous obstruction and radiographic evidence of pulmonary venous congestion. Each patient with significant pulmonary venous obstruction had a soft continuous murmur at the left lower sternal border or xyphoid area, orginating at the site of obstruction in the surgically created pulmonary venous atrium.[21] Therefore, the presence of a continuous murmur after the Mustard operation should suggest significant pulmonary venous obstruction.

Right ventricular dysfunction has been reported in patients who have undergone the Mustard operation and has been documented by angiocardiographic volumetric studies as well as by echocardiography.[15–17] Also, the potential for dysfunction of the tricuspid valve as the systemic atrioventricular valve has often been discussed in the past and a high incidence of tricuspid regurgitation has been reported.[22] However, the incidence of significant tricuspid regurgitation in this study was low and was usually related to closure of a ventricular septal defect through the tricuspid valve, as reported by others.[9,23]

Left ventricular outflow tract obstruction can be a difficult problem in patients with TGA. In our patients a significant gradient between the left ventricle and pulmonary artery was never apparent in the newborn period, even in patients who were subsequently shown to have developed pulmonary stenosis at a later age. It is not uncommon to find a mild to moderate pressure gradient between the left ventricle and pulmonary artery at preoperative cardiac catheterization, and yet have the left ventricular outflow tract appear unobstructed at surgery. Mild to moderate gradients regressed postoperatively in most of our patients, probably because of the decrease in pulmonary blood flow after physiologic correction.

Localized valvular or subvalvular obstruction (discrete subpulmonary membrane or aneurysm of the membranous septum) is rare but was always surgically correctable in our patients. In contrast, diffuse obstruction was not effectively relieved. Fortunately, true tunnel-like subpulmonary stenosis is rare, because surgical relief of such obstruction is quite difficult and may require a conduit from the left ventricle to the pulmonary artery to relieve left ventricular hypertension.

Although the exact nature of the subpulmonary stenosis is difficult to define angiographically, the "4-chamber" view facilitates definition of the left ventricular outflow and is superior to the anteroposterior, lateral, or regular oblique views. Nevertheless, the correlation between the severity of left ventricular outflow obstruction and the angiocardiographic findings is still poor. Because a significant number of patients with pulmonary stenosis, particularly those with pressure gradients <50 mm Hg, improved spontaneously after the Mustard operation, the obstruction was most likely functional. Rarely, the gradient increases postoperatively.[9,24]

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Rest and Exercise Right and Left Ventricular Function Late After the Mustard Operation: Assessment by Radionuclide Ventriculography

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To evaluate ventricular function late after atrial repair of transposition of the great arteries (TGA), 26 asymptomatic patients had rest and exercise radionuclide ventriculography performed a mean of 9 years (range 5 to 15) after undergoing the Mustard operation. The mean resting right (systemic) ventricular (RV) ejection fraction (EF) was 0.50 ± 0.10 (±1 standard deviation); the RVEF was <0.45 in 8 patients. With exercise the RVEF increased in 9 patients and either failed to increase or decreased in 15 (including all 8 patients with resting values <0.45). The weight-adjusted work load performed was a first predictor of RV exercise response (sensitivity 87%, specificity 92%); patients whose RVEF increased did more work.

The mean resting left (pulmonary) ventricular (LV) EF was 0.58 ± 0.09; the LVEF was <0.50 in 3 patients. With exercise the LVEF increased in 14 patients and did not increase in 10 (including all 3 with resting values <0.50). The presence of complex ventricular arrhythmia documented on Holter monitoring was a first predictor of failure of the LVEF to increase with exercise (sensitivity 84%, specificity 71%).

The patient's age, operative age, postoperative interval, residual arterial desaturation, preoperative large ventricular septal defect or pulmonary stenosis, postoperative pulmonary stenosis or superior vena caval obstruction, or performance of a second open-heart procedure was predictive of the rest or exercise EF of either ventricle.

The Mustard operation is a well-established method of relieving cyanosis in patients with transposition of the great arteries (TGA).[1] It is not a true total correction, however, because the anatomic right ventricle remains the systemic ventricle and the anatomic left ventricle the pulmonary ventricle. The long-term effects on the right ventricle of functioning at systemic pressure are not known.[2,3] Previous studies using cardiac catheterization and contrast ventriculography have demonstrated right (RV) and left ventricular (LV) dysfunction in some patients after the Mustard operation.[2–5] Radionuclide ventriculography enables noninvasive measurement of RV and LV ejection fraction (EF) at rest[6–10] and during exercise.[11–18] To evaluate the long-term results of the Mustard operation with regard to ventricular function, rest and exercise radionuclide ventriculography was performed on a group of patients late after they had undergone the Mustard operation for TGA. The relation between rest and exercise EF and clinical data was examined. In addition, radionuclide findings were compared with results from exercise testing and 24-hour Holter monitoring to examine the relation between ventricular function and exercise capacity and ventricular arrhythmias.

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Methods

Patient population: Twenty-six patients who underwent the Mustard operation for TGA and who are being followed at Children's Hospital of Pittsburgh constituted the study group (Table I). There were 17 male and 9 female patients aged 8 to 23 years (mean 13) who were studied 5 to 15 years (mean 9) postoperatively. Their age at the time of the Mustard operation ranged from 2 to 11 years (mean 4); 10 patients were under 3 years of age at the time of repair, but none was <1.8. None had cardiovascular symptoms at the time of testing. Five took cardiac medications for arrhythmias, 3 digoxin alone, 1 digoxin and quinidine, and 1 digoxin and propranolol. One patient had a permanent epicardial pacemaker which had been implanted postoperatively for complete heart block.

Eleven patients had arterial oxygen saturation measured by ear oximetry at rest within 5 months of the radionuclide study. Twenty-two had 24-hour Holter monitoring performed within 33 months (21 within 3 months) of radionuclide study. Each patient had at least 1 postoperative catheterization performed from 18 days to 10 years after surgery (mean 3 years). The time from the most recent catheterization to radionuclide study ranged from 1 to 8 years (mean 5). Operative reports were reviewed for 32 procedures in the 26 patients.

Radionuclide studies—data acquisition: The patients were shown the equipment and were given a brief practice session pedaling the bicycle ergometer. The patient's red blood cells were labeled with technetium-99m pertechnetate using a modified in vivo technique. The stannous pyrophosphate dose was adjusted for the patient's weight and the technetium dose adjusted for the patient's age (See Appendix). A high-count density resting supine radionuclide ventriculogram was obtained in the left anterior oblique projection which provided maximal ventricular separation, using a portable single-crystal gamma camera with a parallel-hole collimator (Dynamo, Picker) interfaced with a dedicated on-line computer (MUGA-CART, Medical Data Systems). A 2-minute image was obtained with the patient's feet in the bicycle pedals and analyzed for adequacy of count density.[19] Supine exercise was performed using a bicycle ergometer (Quinton Instruments). Patients began exercising at 200 kg·m/min with increments in work load adjusted according to a protocol.[20] Patients exercised to a symptom-limited maximum, and all stopped because of fatigue or leg weakness. Leads aVF, V_1, and V_5 were recorded at rest and for at least 5 seconds every minute during the exercise and recovery periods. Cuff brachial blood pressure was recorded at rest and every 2 to 2.5 minutes during the exercise and recovery periods. The patient's heart rate was allowed to stabilize for the first minute of exercise at each stage; radionuclide images were obtained in the left anterior oblique projection during the last 2 to 3 minutes of each stage, with the acquisition time determined from the count analysis of the preexercise image. Patients who required 2.5 minutes of acquisition time exercised for 3.5 minutes at each work level, those requiring 2.25 minutes of acquisition time exercised for 3.25 minutes at each work level, and those requiring 2 minutes of acquisition time exercised for 3 minutes at each work level.

Radionuclide studies—data analysis: Analysis of the scintigraphic data was performed using a general nuclear medicine computer (A^2, Medical Data Systems). All studies were filtered temporally and spatially to enhance edge detection. Preliminary right and left ventricular regions of interest were generated using a semiautomatic computer program and hand-corrected when necessary by 2 experienced observers. Corrected regions were applied over the unfiltered data to obtain the ventricular counts used in the final EF determination. The computer-generated LV background posteriorly and inferiorly was determined, the average counts per pixel were calculated, and the area-normalized background subtracted from each image for both RVEF and LVEF calculation. At least 2 images (rest and peak exercise) from each patient were analyzed independently by each observer and analyzed by 1 observer on 2 different days to insure accuracy and reproducibility. When multiple determinations yielded different values that agreed within 0.05, the values were averaged to provide the final EF result. When the multiple determinations differed ≥0.05, the entire analysis procedure was repeated until agreement was reached. If no reproducible EF could be obtained, the data were excluded from consideration in this study. Using these methods we excluded (1) 1 patient in whom ventricular separation was too poor for quantitative analysis of the entire study, and (2) images at peak exercise in 5 patients, 1 in whom exercise and imaging was terminated before acquisition of sufficient counts for analysis and 4 in whom excessive patient motion caused blurring of the ventricular edges. In these 5 patients the RV and LVEF values from the next highest exercise level were used in this study. In no patient did exclusion of the peak exercise image result in a change in classification of the patient's exercise ejection fraction response. Additionally, exercise values were deleted in 2 patients in whom bigeminy developed with exercise, because the arrhythmias rendered EF determination invalid.

Rest and exercise electrocardiographic data were analyzed for change in heart rate and rhythm with exercise and for the presence of ST-T wave changes at rest as well as during exercise.

Other clinical data: Oxygen saturation was measured noninvasively at rest using an ear oximeter (model 47201A, Hewlett-Packard). Twenty-four–hour ambulatory electrocardiographic monitoring was performed using a dual-channel recorder (Holter II, International Medical) which scanned continuously and recorded for 10 seconds every 2 minutes and during each event, using modified leads V_2 and V_5. Pre- and postoperative cardiac catheterizations were performed.

Statistical analysis: Results are reported as means ± 1 SD. To assess the relation of ventricular function to the patient's age, operative age, postoperative interval, pre- and postoperative defects, ventricular arrhythmias, and exercise work

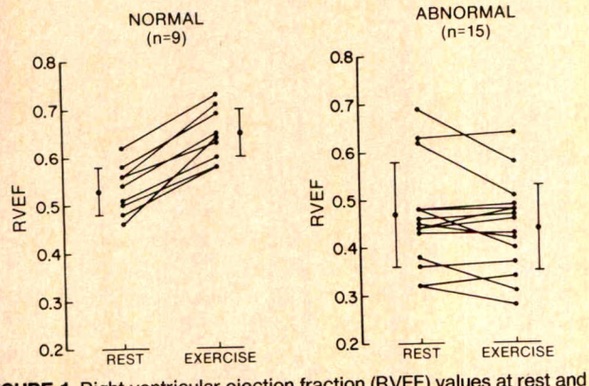

FIGURE 1. Right ventricular ejection fraction (RVEF) values at rest and at peak exercise for the 24 patients whose exercise ejection fractions could be calculated. The mean RVEF was 0.53 ± 0.05 at rest and 0.65 ± 0.05 at peak exercise in the 9 patients whose RVEF increased normally with exercise. The RVEF was 0.47 ± 0.10 at rest and 0.44 ± 0.10 at peak exercise in the 15 patients whose RVEF exercise response was abnormal.

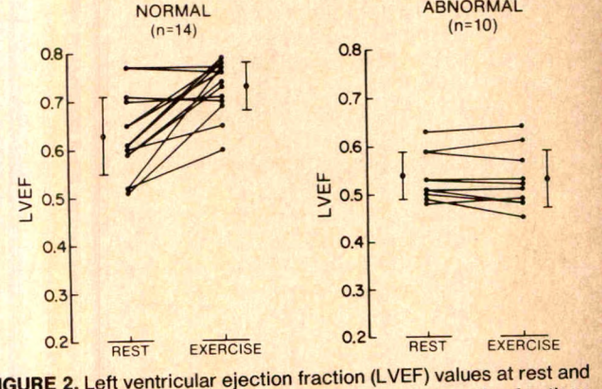

FIGURE 2. Left ventricular ejection fraction (LVEF) values at rest and at peak exercise for the 24 patients whose exercise ejection fractions could be calculated. The mean LVEF was 0.63 ± 0.08 at rest and 0.73 ± 0.05 at peak exercise in the 14 patients whose LVEF increased normally with exercise. The LVEF was 0.54 ± 0.05 at rest and 0.53 ± 0.06 at peak exercise in the 10 patients whose LVEF exercise response was abnormal.

TABLE I Clinical, Exercise, and Ejection Fraction Data in 26 Patients

Case	Age (yr) & Sex	Operative Age (yr)	Medications	Heart Rate (beats/min)		Systolic BP (mm Hg)		RVEF	
				Rest	Exercise	Rest	Exercise	Rest	Exercise
1	20.5M	5.2	None	58	175	120	180	0.56	0.63
2	9.4M	2.8	None	67	135	110	140	0.48	0.58
3	16.5F	7.5	None	80	140	110	160	0.44	0.46
4	11.5M	2.4	Digoxin	74	150	105	145	0.46	0.64
5	15.5M	4.7	None	52	165	105	160	0.50	0.58
6	11.0M	3.3	None	100	160	100	150	0.45	0.42
7	13.3M	2.3	None	84	150	100	150	0.62	0.73
8	10.2M	5.2	None	69	125	110	130	0.51	0.60
9	11.7M	4.2	None	90	Atrial bigeminy	100	100	0.65	. . .
10	8.8M	3.9	None	55	150	85	120	0.63	0.64
11	13.9F	3.6	Digoxin, propranolol	70	115	120	140	0.32	0.28
12	9.8M	3.5	None	62	91	110	120	0.48	0.40
13	11.7M	2.2	None	62	128	110	120	0.32	0.34
14	17.7F	3.3	None	62	140	120	160	0.69	0.58
15	21.1F	5.9	None	50	108	110	175	0.48	0.48
16	17.6F	10.8	Digoxin	48	Ventricular bigeminy	. . .	. . .	0.54	. . .
17	12.4M	1.6	None	74	74	115	130	0.36	0.37
18	12.7M	2.3	None	80	135	120	130	0.43	0.43
19	8.3M	1.8	None	85	150	100	120	0.46	0.47
20	13.3F	2.5	None	75	188	120	150	0.44	0.48
21	16.8M	5.3	None	54	130	120	180	0.54	0.65
22	9.8F	5.0	None	61	128	90	110	0.36	0.31
23	22.8F	8.0	None	74	160	110	120	0.62	0.51
24	10.0F	2.1	None	46	110	110	150	0.58	0.69
25	11.7M	4.7	Digoxin quinidine	55	101	90	130	0.48	0.49
26	10.1M	2.3	Digoxin	50	63	100	110	0.56	0.71

BP = blood pressure; LVEF = left ventricular ejection fraction; O_2 = oxygen; PB = pulmonary band; PH = pulmonary hypertension; PS = pulmonary stenosis; PVO = pulmonary venous obstruction; RVEF = right ventricular ejection fraction; SVO = systemic venous obstruction; TVA = tricuspid anuloplasty; TVR = tricuspid valve replacement; VSD = ventricular septal defect.

load, BMDP (Dixon and Brown, 1979) program P7M, a stepwise discriminant analysis, was used. All predictors were given an equal weight and each ventricle was analyzed separately, grouped by normal and abnormal function as defined by EF. The opposing ventricle also was included in each analysis to determine whether dysfunction in 1 ventricle significantly impairs the other. When comparisons were made between 2 groups, Student's t test for unpaired data was used, with $p < 0.05$ considered as significant.

Definition of normal ejection fraction values: Because all patients with TGA have a reversed ventricular relation, there is no control group from which normal values for RVEF and LVEF can be ascertained. Based on several reports[2,3,10–18,21–24] as well as on this laboratory's experience with patients with other forms of heart disease, the following criteria were used: (1) a resting RVEF ≥ 0.45 and a resting LVEF ≥ 0.50 were normal; (2) an increase ≥ 0.05 in RVEF or LVEF with exercise was normal; (3) if the resting EF was ≥ 0.70, any increase or no change with exercise was normal. An EF increase or decrease < 0.05 with exercise was within the error of the technique and therefore not considered a change.

Results

Radionuclide results: Individual rest and exercise RVEF values are shown in Figure 1. The mean resting RVEF was 0.50 ± 0.10 and ranged from 0.32 to 0.69. The RVEF was < 0.45 in 8 patients (31%); in 4 of these the value was < 0.40. With exercise the RVEF increased ≥ 0.05 in 9 patients, decreased ≥ 0.05 in 4, did not change in 11, and could not be analyzed in 2 because of arrhythmias. The mean RVEF of patients whose exercise EF response was normal was 0.53 ± 0.05 at rest and 0.65 ± 0.05 at peak exercise. The mean EF of patients whose exercise EF response was abnormal was 0.47 ± 0.10 at rest and 0.44 ± 0.10 at peak exercise. The difference between the resting EF of the normal responders and that of the abnormal responders was not statistically significant ($0.10 > p > 0.05$). The RVEF exercise response was abnormal in all 8 patients whose resting EF was < 0.45.

The individual rest and exercise LVEF values are shown in Figure 2. The mean resting LVEF was 0.58 ± 0.09 and ranged from 0.44 to 0.77. The LVEF was < 0.50 in 3 patients (12%). With exercise, the EF increased ≥ 0.05 (or did not change if resting EF was ≥ 0.70) in 14 patients, did not change in 10, and could not be analyzed in 2. In no patient did the LVEF decrease ≥ 0.05 with exercise. The mean LVEF of the patients whose exercise EF response was normal was 0.63 ± 0.08 at rest and 0.73 ± 0.05 at peak exercise. The mean LVEF of patients whose exercise EF response was abnormal was 0.54 ± 0.05 at rest and 0.53 ± 0.06 at peak exercise. The difference between the resting EF of the normal responders and that of the abnormal responders was significant ($p < 0.005$). The exercise response was abnormal in the 3 patients whose resting EF was < 0.50.

TABLE I (Continued)

Case	LVEF Rest	LVEF Exercise	Work Load (kg·m/min/kg)	Associated Defects Preoperative	Associated Defects Postoperative	Ventricular Arrhythmias (Holter)	Reoperation	Resting O_2 Saturation (%)
1	0.61	0.79	19.0	...	SVO	Multiformed	No	...
2	0.77	0.77	14.7	PS	PS	Frequent	PVO	92
3	0.77	0.76	9.4	VSD	...	Occasional	VSD	96
4	0.51	0.69	15.3	...	SVO	Occasional	No	95
5	0.52	0.77	22.3	...	...	Occasional	No	87
6	0.59	0.73	12.7	...	...	None	No	...
7	0.51	0.52	12.1	...	PH	Tachycardia	No	90
8	0.49	0.45	10.4	VSD, PB	...	None	TVR	...
9	0.44	...	...	...	SVO	Occasional	SVO	...
10	0.65	0.78	13.6	...	...	None	No	93
11	0.51	0.48	6.4	PS	...	Frequent	No	96
12	0.53	0.52	10.3	...	...	...	No	...
13	0.59	0.74	9.2	...	...	Rare	No	...
14	0.70	0.71	7.4	...	PS	None	No	94
15	0.52	0.60	8.7	...	...	None	No	...
16	0.53	...	...	VSD, PS	PS	Bigeminy	No	...
17	0.53	0.53	7.1	...	...	Multiformed couplets	No	90
18	0.59	0.57	10.0	...	...	...	No	...
19	0.63	0.64	12.0	PS	SVO	Multiformed couplets	PVO & SVO	...
20	0.48	0.49	13.2	...	...	None	No	...
21	0.65	0.76	16.7	...	...	Couplets	No	...
22	0.71	0.70	13.4	VSD, PB	...	None	No	...
23	0.60	0.65	11.1	...	...	...	No	...
24	0.61	0.78	14.7	...	...	None	No	93
25	0.50	0.48	7.3	...	...	Ventricular bigeminy	TVA	...
26	0.59	0.61	9.6	...	...	...	No	...

Six patients (25%) had a normal EF response to exercise in both ventricles; 7 patients (29%) had an abnormal response in both ventricles. Ventricular response was discordant in 11; 3 (13%) had a normal RVEF and an abnormal LVEF response and 8 (33%) had an abnormal RVEF and a normal LVEF response.

Neither the patient's age at the time of the radionuclide study, the operative age, nor the postoperative interval was predictive of resting dysfunction or of an abnormal exercise response in either ventricle. Dysfunction of 1 ventricle did not predict dysfunction of the other.

Exercise results: Rest and exercise heart rate and systolic blood pressure and the rate-pressure product are given in Table I. The exercise data for the patients grouped according to RV and LV exercise response are summarized in Table II. There was no significant difference in any exercise value between those whose RVEF exercise response was normal and those whose response was abnormal. The patients whose LVEF exercise response was normal had a higher mean systolic blood pressure at peak exercise than did those whose exercise response was abnormal ($p < 0.05$), but the difference in rate-pressure product between the 2 groups was not significant ($0.10 > p > 0.05$).

At rest, 14 patients were in regular sinus rhythm, 10 had marked sinus arrhythmia with or without junctional escape beats, 1 had complete heart block with junctional

TABLE II Heart Rate, Systolic Blood Pressure, and Rate-Pressure Product for Those With Normal and Abnormal RVEF and LVEF Exercise Response*

	RVEF Normal	RVEF Abnormal	p	LVEF Normal	LVEF Abnormal	p
Heart rate						
Rest	62 ± 12	69 ± 13	NS	64 ± 14	70 ± 12	NS
Exercise	134 ± 31	135 ± 25	NS	141 ± 19	124 ± 35	NS
Systolic BP						
Rest	109 ± 7	107 ± 11	NS	108 ± 10	109 ± 10	NS
Exercise	149 ± 21	136 ± 19	NS	148 ± 23	131 ± 12	<0.05
Rate pressure product (10^2)	205 ± 66	185 ± 44	NS	209 ± 45	167 ± 59	NS

* All values mean ± 1 standard deviation.
BP = blood pressure; LVEF = left ventricular ejection fraction; NS = not significant; RVEF = right ventricular ejection fraction.

rhythm, and 1 had complete heart block with a permanent ventricular pacemaker. With exercise, 17 patients had regular sinus rhythm, 3 had marked sinus arrhythmia with junctional escape beats, 1 had complete heart block with junctional rhythm, 1 had sinus rhythm with frequent premature ventricular systoles, 1 had 2:1 atrioventricular block, 1 had atrial bigeminy, and 1 had ventricular bigeminy. The patient with paced rhythm did not change with exercise. The incidence of arrhythmias at rest or during exercise was no greater among patients with an abnormal response than among those with a normal response in each ventricle. Sixteen patients had resting S-T segment and T-wave changes related to right ventricular hypertrophy or to right bundle branch block. In no patient did ischemic S-T segment changes develop during or after exercise.

The peak work load achieved by each patient, in kilogram·meters per minute, was divided by that patient's weight in kilograms to give a maximal weight-adjusted work load performed for each patient (Table I). Patients performing a greater weight-adjusted work load were more likely to have a normal right ventricular exercise response. The weight-adjusted work load was a first predictor of RV exercise response with a sensitivity of 87% and a specificity of 92%. The relation between peak weight-adjusted work load and RV exercise response is illustrated in Figure 3. The relation between exercise response and RVEF held when total weight-adjusted work performed (calculated by multiplying each work level by the duration performed, summing the results, and dividing by body weight) was compared with RVEF exercise response.

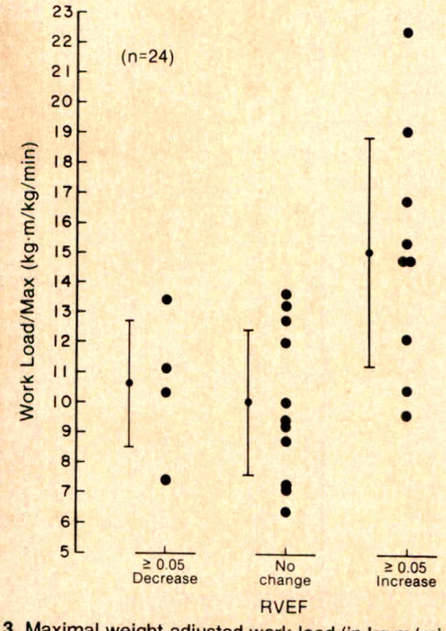

FIGURE 3. Maximal weight-adjusted work load (in kg·m/min/kg) performed plotted against the right ventricular ejection fraction (RVEF) response to exercise for the 24 patients whose RVEF exercise value could be calculated.

Holter monitor results: Of the 22 patients who had 24-hour Holter monitoring, 13 had premature ventricular systoles (Table I). In 4, the premature ventricular systoles were occasional and unifocal. In 9, the ventricular arrhythmias were complex: 2 had frequent premature ventricular systoles, 1 had bigeminy, 4 had multiformed ventricular systoles, 3 had couplets, and 1 had ventricular tachycardia. The resting RVEF of the 9 patients with complex ventricular arrhythmias was not different from that of the other 13 patients (0.48 ± 0.11 versus 0.50 ± 0.11) and the resting LVEF was also not different (0.60 ± 0.09 versus 0.59 ± 0.10). Patients with complex ventricular arrhythmias were more likely to have an abnormal LV exercise response. The presence of complex ventricular arrhythmias was a first predictor of an abnormal LV exercise response with a sensitivity of 84.5% and a specificity of 71.4%. Complex ventricular arrhythmias were not predictive of normal or abnormal RV response.

Other clinical data: Radionuclide data were compared with data obtained at pre- and postoperative cardiac catheterization and noninvasive determination of arterial oxygen saturation. Associated pre- and postoperative defects are listed in Table I. Only ventricular septal defects that would have required therapy had they been the sole defects were included. Pulmonary stenosis was defined as a LV to pulmonary arterial gradient >30 mm Hg. Superior vena caval obstruction was demonstrated either angiographically or by a ≥5 mm Hg gradient between the superior vena cava and systemic venous atrium. No patient had pulmonary venous obstruction, residual ventricular septal defect, patent ductus arteriosus, or hemodynamically significant valvular regurgitation or baffle leak at the time of radionuclide study. None of the following was predictive of an abnormal RVEF or LVEF at rest or exercise: preoperative large ventricular septal defect or pulmonary stenosis, postoperative superior vena caval obstruction or pulmonary stenosis, or resting arterial oxygen saturation <94%. The performance of a second open-heart procedure with cardiopulmonary bypass was also not predictive of abnormal RVEF or LVEF.

Technical considerations: There were several technical problems in performing radionuclide imaging in patients with TGA. RV enlargement necessitated imaging in a steep (75° to 90°) left anterior oblique projection to separate the 2 ventricles, and even then apical septal definition was poor in some cases. Several patients had a small left ventricle, making separation of ventricular activity from pulmonary arterial and atrial activity difficult. Therefore, rest and exercise EF was determined at least twice. Because in most patients the right ventricle contained more counts than the left ventricle, RVEF values were more reproducible.

Discussion

This study demonstrated an abnormal resting RVEF in 8 of 26 asymptomatic patients with TGA who underwent the Mustard operation. In addition, 3 had an abnormal resting LVEF. Right or left ventricular ejection fraction response to exercise, or both, was abnormal

in 18 patients, suggesting a decrease in myocardial reserve.[13–18] The EF is only 1 indicator of ventricular function and is affected by several other factors, such as preload, afterload, and heart rate.[2,5,25–28] In this patient population, however, no differences in any of these factors could be identified to explain the EF changes. Arrhythmias can falsely decrease the EF as measured by equilibrium radionuclide techniques,[29–32] but because the frequency and type of arrhythmias were similar in all groups, arrhythmias alone cannot explain the EF results. Therefore, the EF appears useful as a measure of ventricular function in these patients.

Several hypotheses have been proposed to explain RV dysfunction in these patients. Hagler et al[3] suggested that the structure, the myocardial fiber array, or the pattern of contraction intrinsic to the right ventricle may make it less adaptable to a high afterload. Although this study did demonstrate a high incidence of RV dysfunction, 9 patients had normal RV function at rest and during exercise. This finding argues against an inherent RV problem as the exclusive explanation of RV dysfunction in these patients. Graham et al[2] suggested that histologic damage from ischemia as well as from pressure and volume overload may be responsible for RV dysfunction. This study and the work of others[3,4] did not show any correlation between age at surgical correction and RV function, suggesting that duration of hypoxemia is not the sole explanation for RV dysfunction. However, only 2 of our patients were operated on when <2 years of age and no patient was operated on when <1.5 years of age. Because RV function was not related to patient age in this study, the duration for which the right ventricle has to work against systemic afterload does not appear related to RV dysfunction. However, our oldest patient was 23 years of age, and the possibility that RV dysfunction might be more prevalent in an older population cannot be excluded.

LV dysfunction has been described in some patients after the Mustard operation,[2–4] and Hagler et al[3] reported that it was less frequent in patients who underwent correction at a younger age. This study showed no relation between LV dysfunction and age at correction, but again the patient population did not permit assessment of early corrective surgery. Fewer patients had LV than RV dysfunction.

Several studies have shown that ventricular septal defects and preoperative pulmonary stenosis adversely affect ventricular function.[4,5,31] This study showed no long-term deleterious effect on RV or LV function from either defect. This finding may be consistent with that of Graham et al,[32] who demonstrated a return of increased LV volume measurements to normal in patients with TGA and ventricular septal defect after surgical repair. Our study also found that postoperative pulmonary stenosis, postoperative superior vena caval obstruction, or residual systemic desaturation did not adversely affect RV or LV function.

Several investigators have shown no significant change in ventricular function after the Mustard operation.[2,5] In our study, patients who underwent a repeat open-heart procedure did not have a higher incidence of ventricular dysfunction than did those who did not require reoperation.

Patients with normal RV function as judged by radionuclide angiography performed a significantly greater weight-adjusted work load than did those whose RV function was abnormal. These results indicate that RV function may influence the exercise capabilities of these patients.

Because the presence of complex ventricular arrhythmias predicted an abnormal LV exercise response, it is possible that ventricular arrhythmias are related to LV dysfunction. There was no relation between ventricular arrhythmias and resting RVEF or LVEF or RV exercise response.

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Appendix

The stannous pyrophosphate dose was calculated as follows: 0.2 mg PYP/10 kg body weight. The technetium dose was calculated as follows: (Patient Age + 7 × Adult Dose ^{99m}Tc)/Patient Age + 1.

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Exercise Studies After the Mustard Operation in Transposition of the Great Arteries

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Twenty-one postoperative patients with transposition of the great arteries (TGA) underwent graded exercise testing 4 to 15 years (mean 9) after the Mustard operation. No patient had subjective exercise intolerance before testing, although some had symptomatic resting arrhythmias. Correlations were made between cardiac catheterization data and 24-hour ambulatory monitoring. Exercise tolerance was diminished in nearly half of the patients. No statistically significant differences were found in heart rate or blood pressure responses, but maximal oxygen consumption values were lower than the control values ($p < 0.001$) in the larger patients. Arrhythmias were present or provoked in most patients during exercise testing. Only 28% remained in normal sinus rhythm during and after exercise. Multifocal premature contractions were the most serious arrhythmias demonstrated. Some long-term survivors of the Mustard operation may have abnormal exercise dynamics, even though they may be asymptomatic and have normal physical activities and endurance. Mean maximal systolic blood pressure, heart rate, oxygen consumption, and maximal treadmill times were consistently in the low-normal range or were statistically lower than normal.

Graded maximal exercise testing provides an objective way to measure the exercise capability of patients with congenital heart disease and occasionally discloses abnormalities not clinically apparent in the resting state.[1–13] Such testing is particularly useful in determining the postoperative functional capacity of patients with congenital heart disease, because postoperative resting hemodynamics and other noninvasive studies may not demonstrate significant abnormalities found during exercise. A group of clinically well postoperative patients with transposition of the great arteries (TGA) were tested to determine their exercise endurance,

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maximal oxygen consumption, blood pressure and arterial oxygen responses, and electrocardiographic changes during dynamic exercise.

Methods

Twenty-one patients >8 years of age (8.8 to 22 years, mean 13) underwent graded treadmill exercise testing in the Exercise Physiology Laboratory. These patients who volunteered to participate in the exercise test were selected from a group of 35 asymptomatic patients who had survived ≥3 years after the Mustard operation. Eleven patients had simple TGA, whereas the remainder had additional associated defects including ventricular septal defect (4 patients), pulmonary stenosis (3 patients), or both (3 patients). Age at the time of the Mustard operation ranged between 1.6 and 11 years (mean 4.6), and the postoperative interval ranged from 4 to 15 years (mean 9). No patient had apparent exercise intolerance and all participated in noncompetitive physical activities at the time of their exercise study. Four patients were taking cardiac medications at the time of their exercise study, including digoxin (2 patients), propranolol (1 patient), and both (1 patient).

Sixty-one youngsters without heart disease (range 9 to 20 years, mean 14) constituted the control group which was comprised of normal volunteers and individuals who were tested because of a history of chest pain or a suspected arrhythmia. None was regularly involved in strenuous competitive athletics at the time of the exercise test. The age and sex distributions were comparable in the control and study groups. Both groups were divided into 3 subgroups by body surface area (Group I: 0.7 to 1.09 m^2, 5 patients; Group II: 1.10 to 1.39 m^2, 11 patients; Group III: 1.40 to 1.89 m^2, 5 patients).

Four limb and 6 precordial electrodes were placed after superficial skin abrasion with a dental burr. All patients and control subjects underwent progressive exercise testing on a treadmill using a modified Balke protocol (International Medical Corporation Viagraph I Electrocardiographic Stress Monitor and Treadmill). Eighteen patients walked at 3.4 mph, but 3 younger patients performed at 3.0 mph to prevent running. A 4% increment in treadmill elevation was made every 3 minutes. Resting blood pressure, heart rate, and a 12-lead electrocardiogram were obtained in sitting, standing, and supine positions and after hyperventilation. One precordial lead was continuously monitored (V_1 in the transposition group and V_5 in the control group) during each test and a 12-lead strip was recorded every minute. Blood pressure was obtained every 3 minutes with a programmed sphygmomanometer (Narco Biosystems model PE-300) and an appropriate-sized arm cuff. Oxygen consumption was measured in the sitting position at rest and continuously throughout the exercise test (Waters model MRM-1 Oxygen Consumption Computer). Validation studies comparing this instrument and the Douglas bag method for oxygen consumption by us and others[14] have shown a high correlation in results (r = 0.90) between the 2 methods. In both groups, arterial oxygen saturations were measured noninvasively at rest and during exercise with an ear oximeter (Hewlett-Packard model 47201A). Correlation studies have previously been performed in our laboratory and by others[15] comparing the ear oximeter method and direct blood gas analysis of arterial blood samples obtained during diagnostic cardiac catheterization. In a study of 30 patients (aged 6 to 20 years, mean 12) undergoing elective cardiac catheterization in whom left heart or systemic arterial blood samples were obtained, correlation with noninvasive ear oximeter values was high (r = 0.91).

All patients and control subjects were encouraged to proceed to exhaustion. Monitoring was continued for 6 minutes after exercise or until the patient's vital signs returned to baseline values. Oxygen consumption reached a plateau at the end of exercise.

Cardiac catheterization: All 21 patients had at least 1 postoperative catheterization. This procedure occurred an average of 55 months (range 8 to 86) before exercise study. Intracardiac pressure, oxygen saturation, and cineangiographic studies were performed in all patients. Eleven of the 21 patients also had electrophysiologic studies to evaluate sinus node function, conduction intervals, and response of the atrioventricular (AV) node to rapid atrial pacing.

Twenty-four-hour ambulatory monitoring: Sixteen of the 21 patients with TGA had at least one 24-hour ambulatory electrocardiographic monitoring period with the International Medical Corporation Holter II dual-channel recorder. This unit scans continuously and records a 10-second trace every 2 minutes automatically as well as during any abnormal electrical event.

TABLE I Summary of Exercise Data

Parameter	Group	TGA (n = 21)	Control (n = 61)	p Value
Treadmill time (min)	I	9 ± 4	12 ± 4	NS
	II	11 ± 4	13 ± 3	NS
	III	8 ± 3	16 ± 4	<0.001
Maximal heart rate (beats/min)	I	148 ± 2	172 ± 11	<0.01
	II	156 ± 30	188 ± 10	NS
	III	160 ± 38	189 ± 10	NS
Maximal systolic blood pressure (mm Hg)	I	119 ± 12	129 ± 8	NS
	II	127 ± 19	135 ± 16	NS
	III	132 ± 17	158 ± 23	NS
Maximal oxygen consumption (ml/kg/min)	II	45.8 ± 5	54.2 ± 10	NS
	III	34.0 ± 7	51.1 ± 10	<0.001

BP = blood pressure; NS = not significant; TGA = transposition of the great arteries.

Results

Cardiac catheterization and electrophysiology: These studies were performed from 1 to 9 years postoperatively (mean 4) and demonstrated a variety of hemodynamic abnormalities including superior vena caval obstruction in 3 patients (superior vena cava—systemic venous atrial gradient ≥5 mm Hg); pulmonary venous obstruction in 2 patients (pulmonary capillary wedge-pulmonary venous atrial gradient ≥5 mm Hg); pulmonary stenosis in 4 patients (left ventricular—pulmonary artery gradient ≥50 mm Hg); residual ventricular septal defect in 4 patients; right ventricular dysfunction in 1 patient (resting right ventricular end-diastolic pressure ≥10 mm Hg + poor contractility of right ventricle); interatrial baffle leak in 5 patients. Electrophysiologic studies in 11 patients consisted of measurement of A-H and H-V intervals (7 patients), rapid atrial pacing (10 patients), and sinus node recovery time (10 patients). Of the 10 patients with measured sinus node recovery time, 6 had a normal time (<250 ms, corrected for R-R interval) and in 4 it was prolonged. Nine of 10 patients with rapid atrial pacing had a normal response (1:1 conduction to pacing rates of 200 beats/min). In 1 patient AV block developed at a pacing rate of 140 beats/min. Atropine did not change his maximal pacing rate. Of the 7 patients in whom an

H-V interval could be measured, 5 had normal (H-V <55 ms) whereas 2 had prolonged conduction. Three patients who developed premature ventricular contractions and another who developed junctional rhythm during exercise testing had previously had normal electrophysiologic studies.

Exercise tolerance: Graded exercise tests were performed 8 to 86 months (mean 56) after postoperative cardiac catheterization (Table I). Ten (47%) of 21 patients had decreased exercise tolerance (treadmill time <8 minutes with a maximal oxygen consumption <40 ml/kg/min). No statistically significant difference was seen in the maximal duration of exercise between control Groups I and II and TGA Groups I and II, but a significantly lower treadmill time was apparent in Group III TGA patients compared with Group III normal subjects ($p < 0.001$) (Table I).

Heart rate response: Maximal heart rate was evaluated in 18 of the 21 patients. (Three patients were excluded because of propranolol therapy in 2 patients and a permannent pacemaker in 1.) There was no statistically significant difference in heart rate response between TGA patients and control subjects in all subgroups. However, the TGA groups were at the lower limit of the maximal heart rate range.

Blood pressure response: Maximal systolic blood pressure was determined in 19 of the 21 patients after the Mustard operation (Table I). (Two patients who were receiving propranolol were excluded.) No statistically significant difference was seen between normal subjects and TGA patients. However, the mean systolic blood pressure in each of the TGA groups was at the lower end of the normal range. No significant difference in diastolic blood pressure during exercise was evident between the TGA and the control groups.

Oxygen consumption: Maximal oxygen consumption values are summarized in Table I. Data were not obtained in Group I patients. No significant difference was present between Group II TGA patients and control subjects, but a significantly lower maximal oxygen consumption was found in the larger patients (Group III) after the Mustard operation ($p < 0.001$).

Arterial oxygen saturation: Systemic arterial oxygen saturations were noninvasively determined by ear oximetry in 16 patients during exercise testing. Only 9 patients (56%) had a normal oxygen saturation (>94%) at rest. Of these, 4 developed mild desaturation during exercise (90 to 92%). None of the 4 patients had had any evidence of right-to-left intracardiac shunting by indicator dye dilution study or cineangiography during their previous postoperative cardiac catheterization. Review of their operative notes showed that all 4 had been left with coronary sinus blood draining to the systemic venous atrium. Seven patients were desaturated at rest (75 to 93%). Right-to-left shunts due to interatrial baffle leaks were found in 5 patients at the time of postoperative cardiac catheterization, but 4 of the 7 patients with arterial desaturation had coronary sinus blood draining to the pulmonary venous atrium. Further desaturation developed in all 7 patients with resting arterial desaturation during exercise testing. All normal control subjects had systemic arterial oxygen saturations of ≥95% at rest and during exercise.

Analysis of S-T segments: Only 2 of 21 patients had S-T segment depression of >1 mm at rest. Fourteen of 21 in the TGA group had >1 mm depression of the S-T segment from baseline level in precordial lead V_1 during exercise. In view of preexistent right ventricular hypertrophy in most patients, this S-T segment shift during exercise could not be considered diagnostic of true myocardial ischemia. No abnormal S-T segment shifts were seen in any normal individuals.

Arrhythmias: Abnormal cardiac rhythms were present in 6 patients at rest and became apparent in 5 more during exercise (Table II). Fifteen of 21 patients had sinus rhythm at rest, but only 6 of these 15 remained in sinus rhythm throughout exercise. Premature ventricular contractions were frequently provoked during exercise and occurred in patients who were in normal sinus rhythm (5 patients) or in AV dissociation (1 patient) at rest. One patient with resting multifocal ventricular premature beats continued to show the same abnormality with similar frequency throughout exercise. An additional patient who was in normal sinus rhythm at rest and also during exercise developed extreme sinus bradycardia in the early postexercise period. One other patient with surgically induced complete heart block required implantation of an epicardial artificial pacemaker in the early postoperative period. His paced rate did not change during the exercise test. Atrial tachycardia or flutter was not seen during exercise. No arrhythmia was present in any of the normal control subjects.

Long-term electrocardiographic monitoring: Twenty-four hour ambulatory electrocardiographic monitoring was performed in 16 patients with TGA who underwent exercise testing. In most, arrhythmias found during exercise testing were also seen during the longer recording period. Discordance between ambulatory monitoring and the exercise study occurred in 2 patients. In 1, premature ventricular contractions and brief periods (<4 consecutive beats) of ventricular tachycardia were detected only by ambulatory monitoring, whereas in the other patient, ventricular arrhythmias were found only during exercise testing.

Relation of abnormal cardiac catheterization findings to exercise performance: Abnormal cardiac catheterization findings were observed in 17 of 21

TABLE II Cardiac Rhythms and Arrhythmias

Rest		Exercise
NSR (15)	6	NSR
	2	PAC
	2	Junctional
	4	PVC, unifocal
	1	PVC, multifocal
AV dissociation (3)	2	AV dissociation
	1	PVC, unifocal
Junctional (1)	1	Junctional
PVC, multifocal (1)	1	PVC, multifocal
Complete AV block (1)	1	Complete AV block

AV = atrioventricular; NSR = normal sinus rhythm; PAC = premature atrial contractions; PVC = premature ventricular contractions.

postoperative patients including patients with ventricular septal defect, systemic and pulmonary venous obstruction, pulmonary stenosis, and/or pulmonary hypertension. Decreased work performance was seen in 7 patients with exercise-induced arrhythmias and in 3 of 6 patients who demonstrated arterial desaturation at rest or during exercise, or both. Normal exercise responses were found in only 4 patients who had "normal" hemodynamics during postoperative cardiac catheterization.

Discussion

Graded exercise testing has become an important diagnostic tool and may uncover potentially serious cardiac abnormalities not evident in the resting state. Recent studies in the pediatric population emphasize its usefulness and reproducibility.[9–12] Several long-term studies of patients with TGA who had undergone the Mustard operation have shown hemodynamic and electrocardiographic abnormalities,[1–8,13,16] and some recent reports also document abnormal exercise performance in such patients.[17–19]

All patients in this study were attending school or working, or both, and none reported exercise intolerance. Only 4 were receiving cardiac medications. Despite this apparently normal functional state, during the physical stress of exercise a number of parameters, including duration of exercise, maximal heart rate, systolic blood pressure, and oxygen consumption may be abnormally low, either statistically or in the low range of normal. This subnormal response was particularly evident in older patients. Ear oximetry detected arterial desaturation in each patient with a previously documented right-to-left atrial shunt and discovered desaturation during exercise in several more patients who were fully saturated at rest and in whom no right-to-left shunt had been demonstrated at previous cardiac catheterization. Presumably, small interatrial baffle leaks that became more significant with increased systemic venous return were responsible for the desaturation noted during exercise, although intrapulmonary shunting must also be considered.

A variety of hemodynamic abnormalities were documented in some postoperative patients despite a functionally normal clinical status. These residual problems were occasionally associated with abnormal exercise responses. Two patients with significant postoperative pulmonary stenosis (left ventricular-pulmonary artery gradient >50 mm Hg) had coexistent premature ventricular contractions at rest or during exercise, or both, and both had diminished exercise tolerance (maximal oxygen consumption <30 ml/kg/min and treadmill time <9 minutes). Two patients with a resting systemic oxygen saturation <85% had decreased exercise tolerance. Mild pulmonary hypertension (pulmonary arterial pressure 40/15 mm Hg) in 2 patients and complete superior vena caval obstruction in 2 additional patients did not interfere with exercise performance. Arrhythmias at rest and arterial desaturation, determined during cardiac catheterization or noninvasively, appeared to be predictors of an abnormal exercise response.

Because of preexistent right ventricular hypertrophy in most patients, the resting and exercise electrocardiogram was of no help in suggesting myocardial ischemia. Of particular concern was the frequency of arrhythmias noted during maximal exercise testing. Only 6 (28%) of 21 patients remained in normal sinus rhythm both during and after exercise. Premature ventricular contractions were provoked during exercise in 6 patients, and 2 of these 6 had multifocal premature ventricular contractions. The long-term significance of such arrhythmias is unknown, but 1 patient with exercise-induced unifocal premature ventricular contractions died suddenly 6 months after the study, presumably because of an arrhythmia.

Although 24-hour ambulatory electrocardiographic monitoring may detect many arrhythmias, exercise testing *and* ambulatory monitoring should be performed periodically to detect potentially life-threatening arrhythmias. Whether these arrhythmias are related to a lowered maximal heart rate during exercise or are caused by true ischemia, sinus node dysfunction, or depressed right ventricular function remains unknown.

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Arrhythmias in Transposition of the Great Arteries After the Mustard Operation

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Disorders of rhythm or conduction in patients with transposition of the great arteries (TGA) after the Mustard operation have been widely reported. This study provides a systematic evaluation of the electrophysiologic function of 87 survivors of the Mustard operation at a single institution. Surface electrocardiograms were reviewed in all 87 patients, Holter monitoring data in 26 patients, exercise electrocardiograms in 21 patients, and invasive electrophysiologic data in 61 patients. Surface electrocardiograms showed normal sinus rhythm in 52%, sinus node dysfunction in 27%, and atrioventricular block in 16%. Holter monitoring was obtained in an unselected subgroup of 26 patients who had a mean age of 12 years and a mean interval from operation of 9 years. Sinus node dysfunction was found in 58%, atrioventricular block in 27%, ventricular ectopy in 50%, supraventricular ectopy in 27%, and no abnormalities in only 8%. Intracardiac electrophysiologic evaluation showed a high frequency of abnormal sinus node recovery times and suboptimal response of the atrioventricular conduction system to rapid atrial pacing. When all modalities used in this study were considered, sinus node dysfunction occurred in 47%, ectopy in 34%, and atrioventricular block in 23%. Although only 30% of patients had no evidence of arrhythmia, symptoms of rhythm or conduction disturbances were rare.

One of the most widely recognized problems in patients with transposition of the great arteries (TGA) who have undergone the Mustard operation is the occurrence of arrhythmias. An early report from this institution indicated that 2 of 5 operative survivors had persistent arrhythmias, presumably related to surgical trauma to the sinus node in 1 and the atrioventricular node in the other.[1] Subsequently, various studies have reported the frequency of rhythm or conduction disturbances to be 13 to 100%.[2–9] The most commonly described abnormalities are sinus node dysfunction, supraventricular and ventricular tachyarrhythmias, and, to a lesser extent, atrioventricular conduction disturbances. This study provides a systematic evaluation of the electrophysiologic function of 87 survivors of the Mustard operation at a single institution. The parameters reviewed included surface electrocardiograms in all patients and Holter monitoring, invasive electrophysiologic studies, and exercise electrocardiograms in unselected subgroups.

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Methods

Eighty-seven survivors of the Mustard operation performed at Children's Hospital of Pittsburgh since 1965 had recent surface electrocardiograms available for review. All electrocardiograms from these patients were analyzed, and pertinent data regarding rhythm and conduction were tabulated. The time from operation to the most recent electrocardiogram ranged from 4 months to 15 years (mean 5.6 years).

Twenty-four–hour ambulatory Holter monitoring was performed in an unselected subgroup of 26 patients aged 7 to 22 years (mean 12). They were part of a group of older children who were chosen for more extensive evaluation and were not selected because of symptoms or suspected abnormalities. The interval from operation to Holter monitoring ranged from 4 to 15 years (mean 9). A dual-channel recorder (International Medical Cooperation Holter II) was used. The unit scanned continuously and recorded a 10-second trace every 2 minutes automatically and during each abnormal event.

The following definitions were used in the analysis of the surface electrocardiogram and Holter monitoring data. Sinus node dysfunction was defined as inappropriate sinus bradycardia for age, prolonged sinus pauses, or a nonsinus pacemaker by default, that is, junctional or ectopic atrial rhythm. The specific criteria used are shown in Table I. Ventricular ectopy was categorized as simple or complex on the basis of the modified Lown classification.[10] Grades 2 through 5 were considered complex, whereas Grade 1 ectopic activity (uniform, isolated premature ventricular beats occurring in a frequency <30/h) was considered simple. An exception to this categorization was made for rare couplets which were included

in the simple group. A similar classification was applied to supraventricular ectopy.

Invasive electrophysiologic studies were performed in 61 pre- and postoperative patients as part of the routine cardiac catheterization protocol which included hemodynamic and angiographic evaluation. The postoperative patients ranged in age from 1.5 to 14 years (mean 5.3). The mean postoperative interval until the time of the study was 2.3 years (range 0.3 to 10.7). Standard procedures utilizing 1 or 2 intracardiac electrode catheters were used for His bundle recordings and atrial pacing studies.[11] Atrioventricular conduction was evaluated by His bundle recordings in 32 pre- and 32 postoperative patients, with 13 patients having studies both before and after surgery. The upper limits of normal used in our laboratory for A-H and H-V intervals are 120 and 55 ms, respectively. Incremental atrial pacing was also used to assess atrioventricular conduction integrity in 31 pre- and 45 postoperative patients, including 15 patients who had both. A normal response was defined as 1:1 atrioventricular conduction up to and including an atrial pacing rate of 160 beats/min. Sinus node recovery time was evaluated in 24 pre- and 45 postoperative patients (13 had both) by pacing the right atrium at various rates between 120 and 200 beats/min for ≥30 seconds. The absolute sinus node recovery time was determined by measuring the interval between the last pacing artifact and the first spontaneous sinus recovery time and using the longest interval obtained at the different pacing rates. A corrected sinus node recovery time (absolute sinus node recovery time minus resting sinus cycle length) of ≤275 ms was considered normal.[12] Either a longer corrected sinus node recovery time (CSNRT) or a nonsinus recovery was considered abnormal.

Atrial extrastimulus studies were performed to evaluate refractory periods of the atrium and atrioventricular node in 13 patients, 3 pre- and 10 postoperatively. Standard techniques and normal values as described by Dubrow et al[13] were used. Intraatrial conduction was assessed in 8 patients, 2 pre- and 6 postoperatively, by measuring the conduction time from the high right atrium to the low right atrium (as recorded from a His bundle catheter) during spontaneous sinus rhythm. A normal conduction time was considered to be ≤35 ms.[14]

Twenty-one patients undewent stress exercise testing by treadmill according to a modified Balke protocol. The results of this study are the subject of another report, but rhythm and conduction abnormalities detected during exercise were tabulated and correlated with the results from the other variables evaluated in this study.

Results

Surface electrocardiogram: All patients were in normal sinus rhythm before the Mustard operation except 2 patients who had ectopic atrial rhythms. The only other abnormality of rhythm or conduction noted preoperatively was first degree atrioventricular block in 1 patient. The results of the review of the current electrocardiograms of the 87 survivors of surgery are summarized in Table II. Only 45 patients (52%) remained in normal sinus rhythm. The next largest subgroup consisted of 23 patients (27%) who manifested evidence of sinus node dysfunction. Atrioventricular block was present in 14 patients (16%) and was usually first degree. Two patients had third-degree atrioventricular block, 1 of whom required a permanent artificial pacemaker. Combinations of sinus node dysfunction and atrioventricular block or ectopy occurred in a few patients, but ectopics, either supraventricular or ventricular, in the total group were quite rare.

TABLE I Criteria for Sinus Node Dysfunction

	Heart Rate (beats/min)	
	Day	Night
1. Sinus bradycardia		
Age		
>11 yr	<50	<40
7 to 11 yr	<55	<45
<7 yr	<60	<50
2. Sinus pauses		
Duration >1.75 seconds		
3. Nonsinus pacemaker by default		
Junctional rhythm		
Isorhythmic dissociation		
Ectopic atrial rhythm		

TABLE II Arrhythmias After the Mustard Operation: Current Electrocardiogram

	n	(%)
Normal sinus rhythm	45	52
Sinus node dysfunction	23	27
Atrioventricular block	14	16
First degree	11	
Second degree	1	
Third degree	2*	
SND + PVCs	1	1
SND + 1° AVB	1	1
2° AVB + PVCs	1	1
Supraventricular ectopic beats	2	2
Total	87	100

* One patient had an artificial pacemaker.
AVB = atrioventricular block; PVCs = premature ventricular contractions; SND = sinus node dysfunction; 1° = first degree; 2° = second degree.

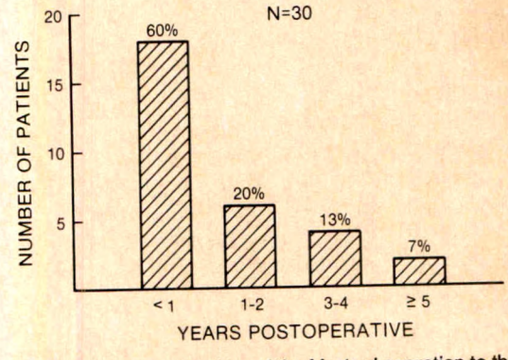

FIGURE 1. Interval from the time of the Mustard operation to the onset of sinus node dysfunction on the surface electrocardiogram.

All electrocardiograms after the Mustard operation until the most recent electrocardiogram also were reviewed and 20 patients showed abnormalities that were not seen on the most recent tracing. The most common finding, occurring in 8 patients, was the bradycardia-tachycardia syndrome with atrial flutter alternating with a slow junctional or sinus rhythm. There were 6 patients who had evidence of sinus node dysfunction on interim electrocardiograms who were in normal sinus rhythm on the current electrocardiogram. Ventricular

TABLE III Arrhythmias After the Mustard Operation: Holter Monitor (n = 26)

Arrhythmias		n	%
Sinus node dysfunction		15	58
Isorhythmic dissociation	7		
Sinus bradycardia	5		
Junctional rhythm	3		
Atrioventricular block		7	27
First degree	2		
Second degree	4		
Mobitz I	1		
Mobitz II	3		
Third degree	1*		
Ventricular ectopy†		13	50
Simple	7		
Complex	6		
Supraventricular ectopy†		7	27
Simple	6		
Complex	1		
Normal		2	8

* Artificial pacemaker.
† Four patients had both ventricular and supraventricular ectopy.

ectopy, supraventricular ectopy, and atrial flutter (without evidence of sinus node dysfunction) were seen in 3 patients each. First degree atrioventricular block was present in 2 patients.

The interval from operation to the first electrocardiographic evidence of sinus node dysfunction could be determined in 30 patients and these results are illustrated in Figure 1. Although 60% of these patients showed sinus node dysfunction within the first postoperative year, 40% had a delayed onset of this abnormality. In half of the latter patients there were no electrocardiographic signs of sinus node dysfunction until ≥3 years after the Mustard operation.

Holter monitor: Results from 24-hour ambulatory monitoring of 26 patients are shown in Table III. As expected, all abnormalities were more frequently seen on Holter monitoring than on routine surface electrocardiography. Sinus node dysfunction was the most common abnormality, occurring in 15 patients (58%). In contrast to the low incidence of ectopy of any kind detected on routine electrocardiograms, 62% of the group undergoing Holter monitoring had ectopy (9 had ventricular alone, 3 supraventricular alone, and 4 both). Thirteen of the monitored group had ventricular ectopy, 6 complex and 7 simple. Supraventricular ectopy was present in 7 patients, but was frequent in only 1. Four patients with supraventricular ectopy also had ventricular arrhthymias. Atrioventricular block occurred in 7 patients (27%) and was first degree in 2, second degree in 4, and third degree in 1. Many patients had a combination of abnormalities and only 2 (8%) in the entire group had 24-hour ambulatory recordings free of any rhythm or conduction disturbances. The Holter technique was superior to the surface electrocardiogram in detecting both sinus node dysfunction and ectopy. A normal surface electrocardiogram was found in 50% of the patients with evidence of sinus node dysfunction on Holter monitoring, whereas only 2 of 17 patients with ectopy were identified by surface electrocardiography. Both Holter monitoring and exercise testing were performed in 17 patients and each was valuable in finding ventricular ectopy. Each technique found patients with significant ventricular dysrhythmias that would have been missed by using only the other method.

TABLE IV Intracardiac Electrophysiology After the Mustard Operation: His Bundle and Rapid Atrial Pacing

	A-H Interval >120 ms		H-V Interval >55 ms		RAP AVB <160 beats/min	
	n	%	n	%	n	%
Preoperative	2/32	6	1/32	3	1/31	3
Postoperative	1/32	3	3/32	9	8/45	18

AVB = atrioventricular block; RAP = rapid atrial pacing.

TABLE V Intracardiac Electrophysiology After the Mustard Operation: Sinus Node Function

	n	%
Normal CSNRT	33	73
Abnormal CSNRT	12	27
Prolonged CSNRT	6	
275–500 ms	4	
>500 ms	2	
Abnormal recovery site	6	
Junctional	3	
Ectopic atrial focus	3	
Total	45	100

CSNRT = corrected sinus node recovery time.

TABLE VI Intracardiac Electrophysiology After the Mustard Operation: Extrastimulus Studies

	Normal	Prolonged n	Prolonged %
Refractory periods (n = 10)			
AERP or AFRP	9*	1	10
AVNERP or AVNFRP	10	0	0
Intraatrial conduction (n = 6)	4	2	33
HRA-LRA			

* Three of these patients had values >1 standard deviation above the mean. Note: One patient had atrioventricular node reentry.
AERP = atrial effective refractory period; AFRP = atrial functional refractory period; AVNERP = atrioventricular node effective refractory period; AVNFRP = atrioventricular node functional refractory period; HRA = high right atrium; LRA = low right atrium.

Intracardiac electrophysiology: Invasive electrophysiologic studies were performed in 61 patients. The results of His bundle recordings and rapid atrial pacing are shown in Table IV. Prolonged A-H or H-V intervals occurred in very few patients either pre- or postoperatively. However, 8 postoperative patients (18%) compared with only 1 preoperative patient (3%) developed atrioventricular block at a pacing rate ≤160 beats/min.

Sinus node function was assessed by using the longest CSNRT obtained by atrial pacing. Twelve of 45 postoperative patients (27%) had an abnormal CSNRT, whereas only 2 of 29 patients (7%) in the preoperative group had abnormal results. Table V illustrates the degree and type of abnormality found in the 12 patients with electrophysiologic evidence of sinus node dys-

function. The large number of patients with abnormal CSNRT correlated with the high incidence of sinus node dysfunction detected by other means, as 67% of these patients had evidence on the surface electrocardiogram or Holter monitor of sinus node dysfunction. However, discrepant clinical and electrophysiologic findings were not unusual. An abnormal CSNRT was present in 13% of those patients with no evidence of abnormal sinus node function on surface electrocardiogram or Holter monitor. Conversely, 21% of those with a normal CSNRT had clinical evidence of sinus node dysfunction.

Atrial extrastimulus studies were performed to evaluate refractory periods of the atrium and atrioventricular node, and intraatrial conduction was also assessed (Table VI). Because normal values were obtained in all preoperative patients, only postoperative data are shown. Although only 1 patient had a prolonged atrial refractory period, defined as >2 standard deviations greater than the mean values determined by Dubrow et al,[13] there were 3 additional patients who had values >1 standard deviation above the mean. None of this group had abnormal AV nodal refractory periods, although in 1 patient Wenckebach block had developed during rapid atrial pacing at 160 beats/min. Intraatrial conduction was prolonged in 2 patients. During the extrastimulus study, 1 patient had readily inducible supraventricular tachycardia with characteristics of AV nodal reentry, although he had no clinically detected arrhythmia.

Combining the results of all modalities used to evaluate electrical function in this study, there was a very high incidence of arrhythmias. Evidence of sinus node dysfunction occurred in 47% and ectopy in 34%. Although atrioventricular block was seen in 23%, only 2 patients had third degree atrioventricular block and only 1 of these required a permanent artificial pacemaker. Only 26 patients (30%) had no demonstrable abnormalities of electrical function.

Discussion

Postoperative disturbances of rhythm and conduction in patients with TGA after the Mustard operation have been widely reported and the frequency has varied between 13 and 100%.[1–9] Several possible explanations exist for this discrepancy in the frequency of abnormalities among the various series, including a varying duration of follow-up, different methods of evaluation (that is, surface electrocardiography, invasive electrophysiologic studies, Holter monitoring, or exercise testing), and lack of agreement on what actually constitutes an abnormality. As expected, ambulatory 24-hour monitoring greatly increases the yield of conduction and rhythm disturbances compared with analysis only of random surface electrocardiograms. However, as Southall et al[5,15] have pointed out, many bradyarrhythmias detected on 24-hour ambulatory recordings in postoperative patients that are presumed to be abnormal may actually occur in a normal population. Further studies on normal children are needed before valid criteria for abnormalities can be firmly established.

The higher frequency of abnormalities detected by ambulatory monitoring also may be related to the longer duration of follow-up since operation in the 24-hour monitored group (mean 9.2 years) than in the group whose electrocardiograms were reviewed (mean 5.6 years). Clearly, the frequency of sinus rhythm decreases as patients are followed up for longer periods postoperatively.[8,16]

The types of arrhythmias that have been described fall into 2 categories, passive or bradyarrhythmias and active or tachyarrhythmias. The former group includes sinus node dysfunction and atrioventricular conduction disturbances, whereas the latter category includes supraventricular and ventricular ectopy. The sites of potential damage during placement of the interatrial baffle include the sinoatrial node and its artery, atrial conduction pathways, the atrioventricular node, and the proximal His bundle. In patients with associated anomalies, such as ventricular septal defect and subpulmonary stenosis, requiring surgical intervention, the infrahisian conduction system and ventricular tissue may also be injured.

Although all factors involved in the pathogenesis of arrhythmias in patients after the Mustard operation may not be completely understood, interruption of normal sinus node function is undoubtedly of major importance. It is not surprising that sinus node dysfunction is the most commonly reported arrhythmia in view of the extensive surgical manipulation required in the vicinity of the sinoatrial node and its artery during the Mustard procedure. Histologic evidence of sinoatrial node degeneration and damage to the sinoatrial node artery has been demonstrated in postoperative patients.[8] This same study showed surface electrocardiographic evidence of sinus node dysfunction in approximately half those patients followed up >3 years. Saalouke et al[4] found that 63% of patients had a prolonged CSNRT on intracardiac electrophysiologic testing, and a study of 52 postoperative patients by Gillette et al[17] demonstrated a 58% incidence of abnormal sinus node recovery after rapid atrial pacing. In the latter study, 3 of 9 patients also had prolonged sinoatrial conduction times.

Although Clarkson et al[2] reported that 87% of their patients remained in normal sinus rhythm after the Mustard operation, their analysis involved only surface electrocardiograms and the average follow-up time was only 31 months. The present study demonstrates that the use of multiple parameters of evaluation and longer duration of follow-up greatly increases the number of abnormalities detected. Both Holter monitoring and intracardiac electrophysiologic testing detected evidence of sinus node dysfunction not present on the surface electrocardiogram and resulted in an overall incidence of 47%. Furthermore, 20% of the patients in this series with surface electrocardiographic evidence of sinus node dysfunction did not show this abnormality until >3 years after the Mustard operation.

Various modifications in surgical technique have been recommended to avoid damage to the sinoatrial node and its artery.[2,3,5,9] Although several series have demonstrated a decrease in the incidence of sinus node

dysfunction after these modifications,[3,9] the occurrence rate of this abnormality remains significant. It is likely that the moderate improvement in results is related more to a heightened awareness of the anatomy and importance of the sinoatrial node and its artery than to any specific changes in technique. At our institution, modifications in the surgical approach to the Mustard operation since the early 1970s have generally paralleled the increased appreciation of the importance of preserving sinoatrial node integrity. These include avoiding cannulation near the superior vena cava-right atrial junction and taking care in suturing the superior portion of the interatrial baffle.

In addition to concern over surgically induced damage to the sinoatrial node, the effect of the Mustard operation on atrial and atrioventricular nodal electrophysiologic function has also been the subject of investigation. Although Gillette et al[17] showed that intraatrial conduction between the high right atrium and the low septal right atrium was abnormal in only 2 of 41 patients studied, several patients had isolated areas of delayed atrial conduction in the low lateral right atrium. Saalouke et al[4] demonstrated a prolonged atrial effective refractory period in 33% of their patients. Both studies showed that atrioventricular nodal function was almost always normal postoperatively. The number of patients who had atrial extrastimulus studies and evaluation of intraatrial conduction in the current series was small, but the occurrence of abnormal atrial refractory periods and prolonged intraatrial conduction in some of these patients indicates that further studies are warranted. Although this series showed a significant number of patients with evidence of abnormal atrioventricular conduction by either surface electrocardiogram or response to rapid atrial pacing, third degree atrioventricular block occurred only twice and only once did it necessitate a permanent artificial pacemaker. Other studies have also shown that atrioventricular conduction disturbances may be found in postoperative patients.[18,19]

Tachyarrhythmias, either supraventricular or ventricular, have also been recognized as a source of morbidity after the Mustard operation.[4,5] In electrophysiologic studies of the cause of supraventricular tachycardia after the Mustard operation, Gillette et al[17] found reentry within either the sinus node or the atrial myocardium to be the predominant mechanism. Although sudden death in patients with a good hemodynamic result from the Mustard operation has been associated with atrioventricular conduction disturbances,[3] it is becoming apparent that ventricular arrhythmias may be an even more important factor in this distressing late complication. Previous studies using ambulatory monitoring showed considerable variation in the frequency of ventricular premature beats or tachyarrhythmias. Hayes et al[16] found that 12% of their patients had multiple premature ventricular contractions, whereas Saalouke et al[4] detected complex ventricular arrhythmias in 40%. The use of Holter monitoring and exercise testing in addition to routine surface electrocardiography demonstrated complex ventricular ectopy in 23% of our patients. No patient in our series has been symptomatic from ventricular arrhythmias and none has received chronic antiarrhythmic therapy, because complex ectopy occurred infrequently during the monitoring period. Recently, however, a 23-year-old woman who had exercise-induced multiform premature ventricular contractions died suddenly. Another 14-year-old boy had an unexplained sudden death that was most likely due to a rhythm or conduction abnormality. He had never been studied by ambulatory monitoring, exercise testing, or invasive electrophysiology, but surface electrocardiograms demonstrated first-degree atrioventricular block and a QRS duration of 0.14 second.

Some series have related the incidence of postoperative rhythm and conduction abnormalities to associated cardiovascular anomalies complicating the surgical repair (that is, closure of a ventricular septal defect or resection of subpulmonary stenosis).[5,20] In this series no significant relation was found between associated anomalies and the incidence of postoperative arrhythmias.

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Summary

JAMES R. ZUBERBUHLER, MD

The reports in this Symposium have detailed some anatomic, hemodynamic, and electrophysiologic abnormalities discovered in 95 survivors of the Mustard operation for complete transposition of the great arteries (TGA). Abnormalities were common and most patients had demonstrable residua, some natural and some iatrogenic. The frequency of residual abnormalities could be viewed as an indictment of intraatrial repair and as support for a change to the "arterial switch" operation. However, few demonstrated abnormalities have required treatment, are currently producing symptoms, or are limiting individuals in their daily activities. No residual anatomic or hemodynamic abnormalities seem life-threatening, although we know little of the potential hazards of the electrical derangements.

There have been 8 late deaths among the 95 survivors: 1 occurred just over 1 month after operation, 3 were related to reoperation for important residual hemodynamic abnormalities, 2 were due to infection not related to the congenital cardiac anomaly or to its surgical repair, and 2 others were sudden, presumably caused by dysrhythmia. Each of the latter had premature ventricular contractions, on a 24-hour electrocardiogram in 1 patient and on resting electrocardiogram in the other. Otherwise, both patients had been thought to have had an excellent result.

My current attitude toward the Mustard operation is one of cautious optimism. However, there is little doubt that attrition will continue among our group of survivors, from dysrhythmia and perhaps from right ventricular failure. Whether the Mustard operation or some other form of intraatrial repair will continue to be widely used will depend on other studies like this one and, even more importantly, on similar studies of patients with other types of repair, including the arterial switch operation. Currently a high operative mortality is associated with the switch operation and it is uncertain whether there will be fewer residua than there are in patients who have undergone intraatrial repair. In our institution intraatrial repair continues to be the operation of choice, although more of the Senning than of the Mustard variety of intraatrial repair is currently being performed, largely because of the personal preference of one surgeon. Whether we continue with the intraatrial repair technique will depend on the appearance of studies detailing the "long-term" results of alternative procedures.

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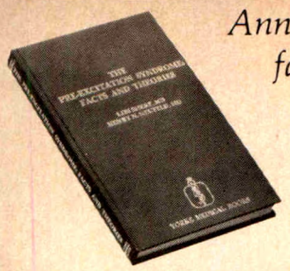

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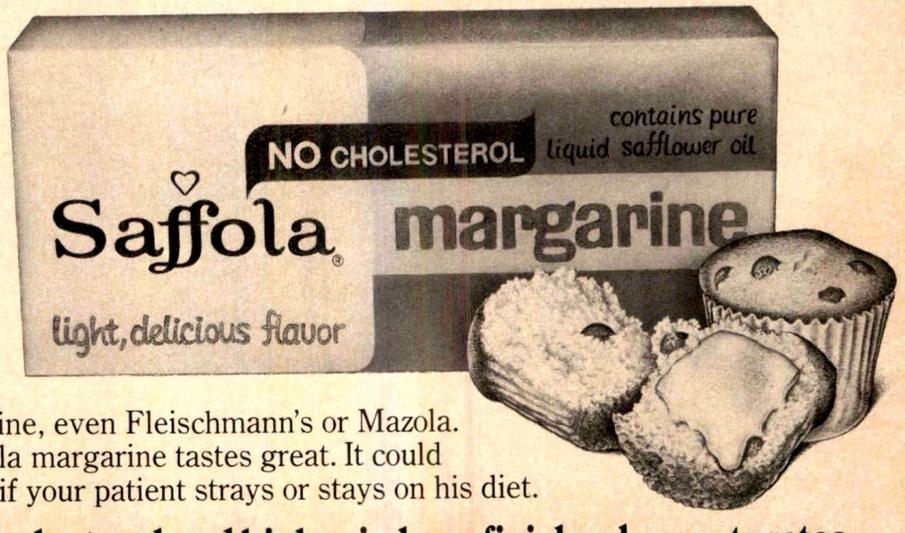

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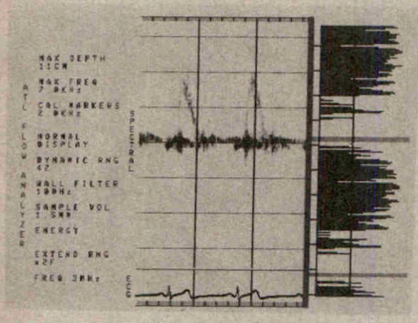

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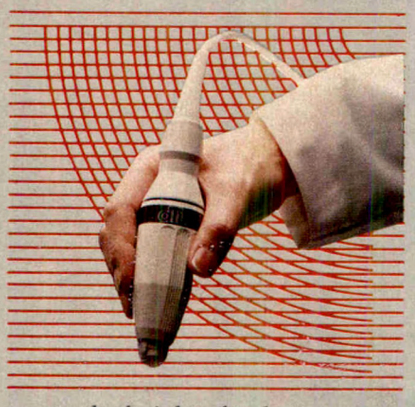

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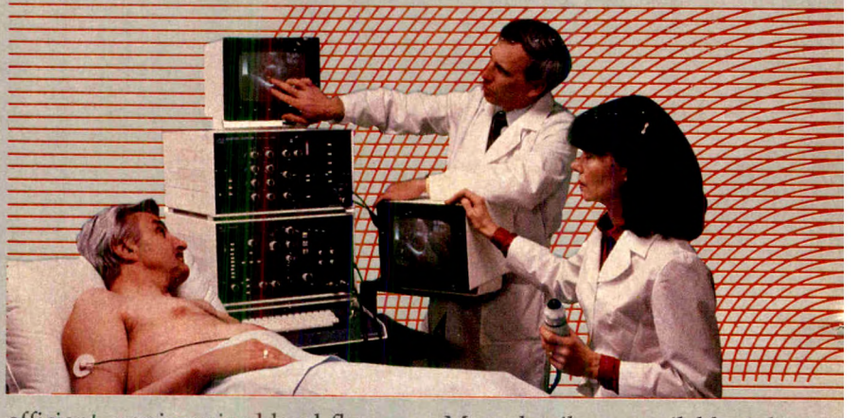

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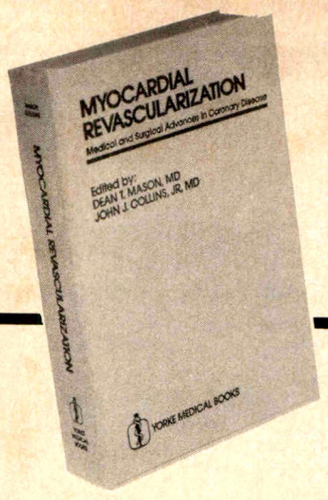

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Your Right to Know... The Facts in Black and White

FACT: Calan® (verapamil HCl) is the calcium antagonist consistently demonstrating antianginal benefits equal to, or greater than, propranolol, at clinically used doses in angina of effort.[1,2,3,4,5,6]

- Calan is also effective in variant angina[7] (where spasm may be exacerbated by propranolol[8]) as well as in unstable angina.[9]

FACT: In direct-comparative studies, the antianginal benefits of Calan were reported to be unsurpassed by nifedipine.[10,11,12]

- In stable effort angina: "The trial demonstrated a clear difference in the antianginal efficacy of [verapamil (Calan) and nifedipine]. . . .Verapamil [Calan] was more effective . . . ."[10] In another study, the efficacy differences were not statistically significant.[11] The doses used in both studies were Calan 120 mg tid and nifedipine 20 mg tid.

  In variant angina, in the one published comparative study, Calan and nifedipine showed equal efficacy. However, this study was neither blinded nor randomized.[12]

- Studies were directly comparative, and responses to each drug were measured objectively.[10,11,12]

FACT: Calan is indicated as single-agent initial therapy for all types of angina, while nifedipine is not.[13,14]

- Nifedipine is indicated in stable effort angina only in patients refractory to or intolerant of nitrates and/or beta-blockers.[14]
- Nifedipine is indicated for unstable angina only when ECG findings indicate vasospasm or the disease is refractory to nitrates and/or beta-blockers.[14]

FACT: The potential serious cardiovascular side effects of Calan are similar to those of beta-blockers.

- Calan and propranolol have basically the same cardiovascular cautions and contraindications such as in patients with ventricular dysfunction, second- or third-degree AV block, or cardiogenic shock.[13,15] Calan is also contraindicated in the presence of sick sinus syndrome or hypotension.
- Calan rarely causes extreme fatigue or mental depression.
- Impotence, memory loss, or nightmares have not been associated with Calan use. Calan may cause constipation.
- Calan can be used without special caution in patients with angina who also have asthma, chronic obstructive pulmonary disease, diabetes mellitus, or peripheral vascular disease such as Raynaud's phenomenon.

FACT: The incidence of adverse effects of Calan and nifedipine merits comparison (see chart below).

Adverse Reactions Reported	nifedipine — Uncontrolled U.S. experience in 2,100 patients. The incidence of adverse reactions in controlled studies was generally the same or higher.[14]	(Calan) verapamil — Clinical studies in 1,166 patients — NOTE that similar results were seen in both controlled clinical trials and uncontrolled clinical experience.[13]
Dizziness, light-headedness	About 10%	3.6%
Constipation	2% or less	6.3%
Flushing	About 10%	*
Headache	About 10%	1.8%
Weakness	About 10%	*
Fatigue	*	1.1%
Nausea	About 10%	1.6%
CHF or pulmonary edema	**	0.9%
Peripheral edema	About 10%	1.7%
AV block: third-degree	*	0.8%
Transient hypotension	About 5%	2.9%
Palpitation	About 2%	*
Bradycardia: HR<50/min	*	1.1%
Syncope	About 0.5%	<0.5%

*Not reported in the prescribing information.[13,14]

**About 2%, "not readily distinguishable from the natural history of the disease." "It remains possible, however, that some or many of these events were drug related."[14]

Calan® (verapamil HCl) **TABLETS** 80 mg and 120 mg

Effective Angina Therapy

Please see reverse side for a brief summary of the complete prescribing information.

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The Facts of Effective Angina Therapy

FACT: Calan® (verapamil HCl) has pharmacologic effects complementary to those of nitrates.[13]

- Like propranolol, Calan decreases myocardial contractility. Calan's effect on the SA node tends to minimize heart rate response to arterial vasodilation, leaving the rate unchanged or slightly reduced.[13]
- Nifedipine tends to cause slightly increased heart rate due to a sympathetic response to arterial dilation.[14]

FACT: Calan provides truly additive effects with propranolol when such combination therapy is necessary in the treatment of chronic stable angina.[3,4]

- In two studies involving a total of 33 patients, the additive effects of Calan with propranolol on exercise tolerance could be seen.

	Study A[3]	Study B[4]
Propranolol alone	+2 min *	+1.3 min
Calan alone	+3.2 min	+3.4 min
Calan with propranolol	+5.3 min	+4.7 min

*Difference from placebo to maximally tolerated exercise

- Combined therapy should be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Because of the still limited experience with combination therapy, Calan should be used alone, if possible.

FACT: Safety considerations are important with Calan, beta-blockers, and nifedipine.

- In patients with normal conduction, Calan's electrophysiologic effects are rarely clinically important.[13] However, Calan's contraindications include patients with sick sinus syndrome or second- or third-degree AV block.
- The concomitant use of digitalis with Calan or nifedipine requires caution because digoxin serum levels may increase.[16,17]
- Both Calan and nifedipine, as well as propranolol and nitrates, require monitoring during upward dose titration.[13,14,15]

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- Calan is the calcium antagonist with consistently demonstrated antianginal benefits equal to or greater than propranolol.
- Calan is effective in variant angina where spasm may be exacerbated by propranolol.[8]
- Calan, unlike nifedipine, has a first-line indication for stable effort angina.

FACT: All the above statements are supported by published materials.

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Contraindications: Severe left ventricular dysfunction (see *Warnings),* hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Occasional elevations of liver enzymes have been reported; patients receiving verapamil should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil. **Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefuly monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR< 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** Calan (verapamil HCl) is supplied in 80-mg and 120-mg sugar-coated tablets.

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Trial of Combined Warfarin Plus Dipyridamole or Aspirin Therapy in Prosthetic Heart Valve Replacement: Danger of Aspirin Compared With Dipyridamole

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Despite the use of oral anticoagulation in patients with prosthetic heart valves, persistent thromboembolism over time warrants a search for improved methods of prevention. Thus, patients receiving 1 or more mechanical prosthetic heart valves were randomized to therapy with warfarin plus dipyridamole (400 mg/day) or warfarin plus aspirin (500 mg/day) on the basis of location and type of valve and surgeon, and followed up with a concurrent, nonrandomized control group taking warfarin alone. In 534 patients followed up 1,319 patient-years, excessive bleeding (necessitating blood transfusion or hospitalization) was noted in the warfarin plus aspirin group (23 of 170 [14%], or 6.0/100 patient-years) compared with warfarin plus dipyridamole (7 of 181 [4%], or 1.6/100 patient-years, p <0.001), or warfarin alone (9 of 183 [5%], or 1.8/100 patient-years, p <0.001). A trend was evident toward a reduction in thromboembolism in the warfarin plus dipyridamole group (2 of 181 [1%], or 0.5/100 patient-years) as compared with warfarin plus aspirin (7 of 170 [4%], or 1.8/100 patient-years), or warfarin alone (6 of 183 [4%], or 1.2/100 patient-years). Adequacy of anticoagulation (based on 12,720 prothrombin time determinations) was similar in all 3 groups with 65% of prothrombin times in the therapeutic range (1.5 ≤prothrombin time/control ≤2.5), 30% too low, and 5% too high. Warfarin plus aspirin therapy resulted in excessive bleeding and is contraindicated. Longer follow-up study is needed to determine whether further separation of the incidence of thromboembolism can be detected.

Thromboembolism in patients with mechanical heart valves remains a major time-related problem. Only 58% of patients with mitral and aortic Starr-Edwards prostheses were free of thromboembolism at 15 years.[1] Although the incidence of thromboembolism has been decreasing in patients with more recent models of prostheses[1] and more recent operations,[2] it remains undesirably high in patients on conventional anticoagulant therapy alone.[1–10] Thus the use of an anticoagulant plus a platelet inhibitor was tested in 6 completed prospective trials.[5–10] Patients given the anticoagulant agent plus either dipyridamole[5–8] or aspirin[9,10] had the lowest incidence of thromboembolism. In 1 study, results did not reach statistical significance. Aspirin has been used in only a small number of patients and never compared with dipyridamole. With the use of aspirin, excessive bleeding ensued with a dosage of 1 g/day[10] but not with 500 mg/day.[9] Therefore, we began a prospective, randomized clinical trial of an orally administered anticoagulant agent plus either dipyridamole or medium-dose aspirin. We report the initial results.

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Methods

From February 1979 to June 1981, patients receiving a mechanical prosthetic heart valve (aortic, mitral, or both) were randomized to treatment with warfarin sodium plus dipyridamole or warfarin sodium plus aspirin on the basis of location of valve (aortic, mitral, or both), type of valve (Starr-Edwards, Björk-Shiley, or other), and name of surgeon. A randomized control group treated with warfarin alone was not a part of the original protocol because we believed that

TABLE I Baseline Patient Characteristics (All Values Are Percentages)

	Warfarin + ASA (n = 170, Median Age 60 yr)	Warfarin + DIP (n = 181, Median Age 59 yr)	Warfarin (n = 183, Median Age 61 yr)
≥70 years old	18	19	12
Male patients	64	60	54
Mitral valve only	31	32	36
Aortic valve only	56	52	53
Mitral and aortic valves	13	16	11
Other associated surgical procedure*	50	46	51
Prior cardiac operation	16	20	26
Prior thromboembolism	7	8	5
Left atrial enlargement†	65	69	68
Atrial fibrillation			
Preoperative	28	36	28
Postoperative	34	31	25
LA thrombus at operation	5	3	5
Mitral valve only			
Starr-Edwards	55	62	64
Björk-Shiley	43	38	33
St. Jude	2	. . .	3
Aortic valve only			
Starr-Edwards	23	23	36
Björk-Shiley	72	73	58
St. Jude	5	4	6
Both aortic and mitral valves			
Both Starr-Edwards	14	48	35
Both Björk-Shiley	67	40	49
Both St. Jude	0	4	4
Combinations	19	8	12

* Most often, aortocoronary bypass operation; second in frequency, tricuspid valve anuloplasty.

† Determined with M-mode echocardiography (>40 mm in size) or plain chest roentgenography.

ASA = acetylsalicylic acid; DIP = dipyridamole; LA = left atrial.

treatment with more than warfarin alone was needed. However, within a few months of starting randomization, we decided to retrieve a control group treated with warfarin alone from patients who had had prosthetic valve replacement starting 2 months before the onset of our study and patients inadvertently not randomized by the surgical services. Thus we have 3 treatment groups for follow-up comparison: (1) warfarin plus dipyridamole 100 mg orally 4 times a day; (2) warfarin plus aspirin 250 mg orally twice a day; and (3) warfarin alone. Anticoagulant therapy and platelet-inhibitor therapy were started 48 hours after operation. Patients with peptic ulcer disease, previous gastrointestinal bleeding, or a bleeding disorder were excluded from the study.

Follow-up endpoints and information (obtained from patients and their physicians every 3 to 6 months) included the following: (1) thromboembolism, (2) bleeding necessitating blood transfusion or hospitalization, (3) adverse effects or problems necessitating discontinuation of the platelet-inhibitor therapy, (4) adequacy of anticoagulation based on prothrombin time determinations, and (5) taking platelet-inhibitor therapy regularly (>95% said yes, consistent with previous objective tests in Mayo Clinic patients[14] and with need for new supplies of platelet-inhibitor drug provided free of charge every 6 months). No blood levels or urine tests of compliance were done. If patients were not reexamined at the Mayo Clinic, hospital records were requested for documentation of thromboembolism or bleeding. Follow-up in this report is through August 1981, when aspirin was stopped because of bleeding (endpoint 2, above).

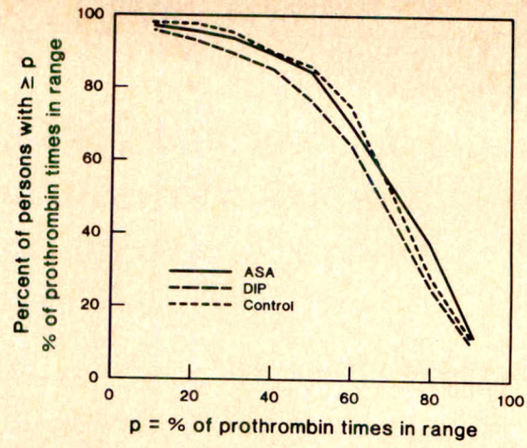

FIGURE 1. Adequacy of anticoagulation in the 3 treatment groups. The **abscissa** shows the percentage of prothrombin times in range ($1.5 \leq x \leq 2.5$). The **ordinate** shows the percentage of patients with at least the percentage of prothrombin times in therapeutic range as indicated on the **abscissa.** For example, 50% of patients had ≥70% of their prothrombin times in the therapeutic range. The percentage of persons with a given percentage of prothrombin times in therapeutic range did not differ significantly in the 3 groups. ASA = acetylsalicylic acid; DIP = dipyridamole.

Thromboembolism was defined as a temporary or permanent neurologic deficit of sudden onset with focal motor weakness or visual deficit unexplained by other factors. Thromboembolic events were tabulated starting immediately after platelet-inhibitor and anticoagulant therapy were initiated. Twenty-three patients died within 48 hours of operation and thus could not be entered. Two patients were excluded from the study because of cerebral emboli (completed stroke) 1 and 2 days after operation before antithrombotic therapy was started. Cerebral bleeding was confirmed either at autopsy or by a computed tomographic scan. A single valve thrombosis was verified at autopsy.

Operations were performed with the use of cardiopulmonary bypass and systemic hypothermia to 20° to 25°C. Multidose, cold (4°C) potassium cardioplegia was used for myocardial protection. The location and type of valve is shown in Table I. The Starr-Edwards valves were of the 6120 and 1260 series (bare strut, Silastic ball) in the mitral and aortic positions, respectively.

Standard chi-square tests were used in the group comparisons.

Results

Patient data (Table I): The baseline characteristics of the 534 patients in the 3 treatment groups are shown in Table I. There were only minor differences among the 3 groups. The main risk factors for thromboembolism, (prior thromboembolism, left atrial enlargement, atrial fibrillation, and left atrial thrombus observed at operation) also show only minor differences.

Adequacy of anticoagulation (Fig. 1, Table II): There were 12,720 prothrombin times and corresponding control values tabulated during the follow-up period. Adequacy of anticoagulation was not different in all 3 groups. In approximately 50% of patients in all 3 groups, ≥70% of their prothrombin times were in the therapeutic range ($1.5 \leq$ prothrombin time/control ≤ 2.5) (Fig. 1). Of all the prothrombin times approxi-

TABLE II Adequacy of Anticoagulation for Patients With and Without Thromboembolism or Bleeding*

	Prothrombin Times (%)					
	No Thromboembolism (n = 519)			Thromboembolism (n = 15)		
	Low	In Range	High	Low	In Range	High
ASA	29	67	4	46	52	2
DIP	33	63	4	75	25	0
Warfarin	28	67	5	35	47	18
Total	30	66	4	41	49	10
	No Bleeding (n = 495)			Bleeding (n = 39)		
	Low	In Range	High	Low	In Range	High
ASA	28	68	4	33	61	6
DIP	34	62	4	20	60	20
Warfarin	28	67	5	11	77	12
Total	30	66	4	24	65	11

* Defined by prothrombin time/control, <1.5 = low, ≥1.5 to ≤2.5 = in range, >2.5 = high.
Abbreviations as in Table I.

TABLE III Thromboembolism and Episodes of Bleeding*

			Thromboembolism			Bleeding					
Group	N	Pt-Yr	n	Per 100 Pt-Yr	Pro T↓	GI	Cerebral	Other	n	Per 100 Pt-Yr	Pro T↑
W + ASA	170	386	7	1.8	2/7	15	5	3	23	6.6§	8/23
W + D	181	427	2	0.5‡	2/2	4	0	3	7	1.6	3/7
W	183	506	6	1.2	3/6	1	3	5	9	1.8	4/9
Total	534	1,319	15	. . .	7/15†	20	9	11	39	. . .	15/39

* Adjustment for type and location of valve resulted in only trivial changes. All thromboemboli were located in the brain or retina, including 1 associated aortic valve thrombosis, and all were during the first year of follow-up except for 2 in the ASA group (year 2) and 1 in the control group (year 3).
† Unknown in 2 patients.
‡ $p > 0.05$ compared with each of the other 2 groups.
§ $p < 0.001$ compared with each of the other 2 groups.
ASA = acetylsalicylic acid; D = dipyridamole; GI = gastrointestinal; Pro T↓ = prothrombin time/control <1.5; Pro T↑ = prothrombin time/control > 2.5; Pt-Yr = patient-years; W = warfarin.

mately 65% were in the therapeutic range, 30% were low, and 5% were high in all 3 groups.

Bleeding and thromboembolism (Tables III and IV): Bleeding episodes were mainly gastrointestinal or intracerebral and predominated in the group taking aspirin ($p < 0.001$). All patients with intracerebral bleeding died. The prothrombin time at the time of hospital admission for bleeding was >2.5 times the control value in a similar percentage of patients in all 3 groups (15/39 or 38% overall, Table III). Patients with bleeding (except those taking aspirin) had more high prothrombin times, $p > 0.05$ (Table II). Because of the excessive bleeding, aspirin was discontinued in all patients in August 1981, and patients were advised to continue taking warfarin alone.

The reduced incidence of thromboembolism in the warfarin plus dipyridamole group did not reach statistical significance. All but 3 thromboemboli occurred during the first year after operation. Thromboemboli occurred as early as 8 days after operation in patients receiving antithrombotic therapy, but 1 and 2 days after operation in 2 patients excluded from the study before starting antithrombotic therapy. Seven of the 15 epi-

TABLE IV Thromboembolism and Bleeding: Actuarial Analysis of Events*

	Warfarin + ASA (n = 170)		Warfarin + DIP (n = 181)		Warfarin Only (n = 183)	
Year	n†	%	n†	%	n†	%
Percent Survivorship Free of Thomboembolism						
1	149	98	164	99	166	97
2	85	96	110	99	135	97
3	20	96	28	99	81	97
Percent Survivorship Free of Bleeding						
1	141	89‡	160	97	170	98
2	80	86‡	103	96	134	95
3	16	86‡	23	96	80	95
Percent Survivorship Free of Thromboembolism and Bleeding						
1	138	87‡	158	95	165	95
2	76	84‡	103	95	129	91
3	15	84‡	23	95	77	91

* Deaths without event are withdrawn alive.
† Number still under observation without event.
‡ $p < 0.01$ compared with each of the other 2 groups.
ASA = acetylsalicylic acid; DIP = dipyridamole.

TABLE V Adverse Effects or Problems Necessitating Cessation of Platelet-Inhibitor Therapy

	Warfarin + ASA (n = 170)	Warfarin + DIP (n = 181)
Gastrointestinal bleeding or ulcer	15	6
Gastrointestinal upset	6	2
Melena	3	1
Headache or dizziness	0	3
Gross hematuria	1	2
Ecchymoses/epistaxis	10	2
Thromboembolism	2	1
Rash	0	1
Other	11	7
Total	48 (28%)	25 (14%)

ASA = acetylsalicylic acid; DIP = dipyridamole.

sodes (47%) resulted in a permanent neurologic deficit, and 5 resulted in death. One patient in the warfarin plus aspirin group with adequate anticoagulation fell down his basement stairs, struck his head, had right leg weakness and a skull fracture, and became comatose and died within 24 hours. Autopsy showed a thrombosed Björk-Shiley aortic valve. Of the 15 patients with thromboemboli, 9 had mitral valve replacement, 5 had aortic valve replacement, and 1 had both. The prothrombin time was low (Table III) at the time of the thromboembolic episode in 7 of 15 patients. There was a trend toward more low prothrombin times in patients with thromboembolism (Table II).

Reasons for cessation of platelet-inhibitor therapy: The reasons for cessation of therapy are listed in Table V. Most of these decisions were made by the local physician. All of these patients are included in the analysis of thromboemboli and bleeding.

Discussion

The preliminary results of this prospective, randomized trial of warfarin plus dipyridamole in comparison with warfarin plus aspirin show the danger of bleeding from warfarin plus regular aspirin use at 500 mg/day and a trend toward a reduction in thromboembolism in the warfarin plus dipyridamole group. The dose of platelet-inhibitor therapy, the adequacy of anticoagulation, and the design of the trial will also be discussed.

Bleeding: Therapy with anticoagulant plus aspirin was compared with therapy with anticoagulant alone in only 2 previous prospective, randomized trials with smaller numbers of patients.[9,10] No severe bleeding was seen in 57 patients treated with anticoagulant therapy plus aspirin at 500 mg/day after follow-up for a mean of 2 years, although 4 (7.0%) of 57 patients had melena as compared with only 1 (1.5%) of 65 patients on anticoagulant therapy alone.[9] In another study,[10] gastrointestinal bleeding occurred in 11 (14.7%) of 75 patients taking anticoagulant therapy plus 1 g of aspirin per day in contrast to 2 (2.7%) of 73 patients taking only an anticoagulant agent. Our results in a large group of patients substantiate the increased risk of bleeding when even a medium dose of aspirin (500 mg/day) is added to anticoagulant therapy. Patients taking anticoagulant therapy should not use aspirin.

Thromboembolism: No previously reported clinical trial has compared therapy with anticoagulant plus dipyridamole with therapy with anticoagulant plus aspirin. Our study showed a trend toward reduction in thromboembolism in the warfarin plus dipyridamole group compared with the warfarin plus aspirin or warfarin alone groups. These results are consistent with previous clinical trials that compared therapy with anticoagulant therapy plus dipyridamole with anticoagulant therapy alone.[5–8] The rate of thromboembolism in the anticoagulant plus aspirin group (1.7/100 patient-years) is similar to the aspirin groups in the study of Altman et al[9] (1.8/100 patient-years) and Dale et al[10] (2.5/100 patient-years), but the rate in our anticoagulant alone group (1.5/100 patient-years) is lower than those from Altman et al (9.3/100 patient-years) and Dale et al (10.7/100 patient-years). The low rate of thromboembolism may in part reflect the decreasing rate observed in recent years as valve design has improved[1] and valve replacement is performed earlier in the course of the valvular disease.[2] Nevertheless, thromboembolism is a continued, cumulative risk that increases over a period of years, involves the cerebral circulation in more than 85% of clinical emboli, leads to a permanent neurologic deficit in 50% of patients, and leads to death in 10%.[1]

Platelet deposition starts intraoperatively on the sewing ring in the canine model.[11] Because we observed thromboemboli causing stroke within 48 hours after operation before anticoagulant therapy could be started, platelet-inhibitor therapy should probably be administered 1 to 2 days before operation and as well as immediately before and after operation (similar to the rationale for perioperative platelet-inhibitor therapy in aortocoronary bypass surgery[13,14]). Preoperative and intraoperative use of dipyridamole has been shown to be safe,[12–14] but preoperative use of aspirin appears to increase bleeding[15] in patients undergoing cardiopulmonary bypass surgery.

Reasons for no reduction of thromboembolism in the anticoagulant plus aspirin group as compared with the anticoagulant alone group are unknown, but contributing factors may be the lack of randomization in the latter group, the small number of clinical events to date, or a low incidence of responders in the aspirin group.[16]

Dose of platelet-inhibitor therapy: The aspirin dosage twice daily was chosen to reproduce the trial by Altman et al.[9] The optimal dose of aspirin alone appears to differ from the optimal dose to be combined with dipyridamole.[16,17] The dose of dipyridamole was chosen because of the success in previous trials[5–8] and the necessity for a larger dose to prolong a shortened platelet survival when used alone without aspirin.[17]

Adequacy of anticoagulation: Adequacy of anticoagulation appears to influence the thromboembolic risk after prosthetic (especially mitral) valve replacement.[1,3,18] Friedli et al[18] found that when more than 15% of the total number of prothrombin times in a patient

were too low (<1.5 times the control value), the rate of thromboembolism increased greatly. Only 19% of their patients (16% of our patients) had this ideal control, less than 50% their (and our) patients had ≥75% of their prothrombin times in therapeutic range, and 56% of their patients (47% of ours) with a thromboembolic event had a low prothrombin time at the time of the event. The adequacy of anticoagulation in our patients (Fig. 1, Table II) was very similar in the 3 treatment groups and was also very similar to results in the patients of Friedli et al studied nearly 10 years ago.

Similarly, an increased risk of bleeding is present when the prothrombin time is too high.[19] Approximately 50% of patients in the report by Forfar[19] and 40% of our patients with bleeding had a prothrombin time >2.5 times the control value at the time of the event. The adequacy of anticoagulation achieved and the relationship of thromboembolism and bleeding to this adequacy emphasizes the difficulty of and the need for good anticoagulant control.

No intracerebral bleeding has been seen so far in the warfarin plus dipyridamole group despite similar anticoagulant control, raising a question of whether preexisting cerebral thromboembolism may predispose to intracerebral bleeding. Thus, a reduction in cerebral thromboembolism might then lead to a reduction in intracerebral bleeding.

Trial design: The ideal clinical trial should be prospective, randomized, double-blind, placebo-controlled with the appropriate dose and timing of drug administration, and of adequate size and duration to have sufficient patients with a sufficient number of events defined as endpoints for meaningful subgroup analysis.[13,20] Patients should be adequately characterized to ensure that the risk factors influencing the endpoints are equal in all treatment groups.[13]

This trial was not blinded or placebo-controlled, and compliance was not assessed by pill counts or urine tests. Initially a randomized control group was not included because the addition of a platelet-inhibitor had lowered the high incidence of thromboembolism in previous trials,[5,6,9,10] but a decreasing incidence of thromboembolism in the last few years[2] makes a randomized control group very important. Platelet-inhibitor therapy should probably be started before operation and given immediately before and after operation to minimize the early postoperative risk of thromboembolism. The safety of starting dipyridamole before operation has been documented,[12–14] but the hypothesis of reducing early thromboembolism needs to be tested in a new clinical trial.

Despite the absence of randomized, placebo control subjects and a subjective inquiry for compliance, the adequacy of anticoagulation was similar in all groups, and preliminary results show excessive bleeding in the warfarin plus aspirin group. There was also a trend toward a reduction of thromboembolism in the warfarin plus dipyridamole group as compared with the warfarin plus aspirin group. All aspirin in our patients has been discontinued, and follow-up will continue for 3 to 4 more years to see whether further separation of the groups can be detected.

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Early Detection of Left Ventricular Dysfunction in Chronic Aortic Regurgitation as Assessed by Contrast Angiography, Echocardiography, and Rest and Exercise Scintigraphy

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The best method for detecting early left ventricular (LV) dysfunction in patients with chronic aortic regurgitation is uncertain. Variables used previously to identify LV dysfunction have included (1) angiographic measurements to identify an LV end-systolic volume index (LVESVI) $\geq$60 ml/m^2, (2) echocardiographic measurements to identify LV end-systolic dimension (LVESD) $\geq$5.5 cm or LV fractional shortening $\leq$25%, and (3) depressed LV ejection fraction (EF) at rest and/or an LVEF or LVESVI that deteriorates with exercise as detected by myocardial scintigraphic measurements. The hypothesis was tested that radionuclide ventriculography with exercise allows earlier detection of important LV dysfunction in patients with aortic regurgitation than the other variables. In 15 consecutive asymptomatic or only minimally symptomatic patients (8 men and 7 women, mean age 44 years) with isolated 2 to 4+ aortic regurgitation (1) rest and exercise-gated radionuclide ventriculography, (2) M-mode echocardiography, and (3) LV angiography were performed. No other cause of LV dysfunction was apparent in 13 patients; 1 patient had moderate systemic arterial hypertension and 1 had 50% luminal diameter narrowing of the proximal left anterior descending coronary artery. Ten patients did not have an increase in LVEF >0.05 EF units at peak exercise (0.58 $\pm$ 0.11 to 0.50 $\pm$ 0.12, mean $\pm$ standard deviation [SD]) (Group 2), whereas 5 had a normal LVEF response to exercise (0.63 $\pm$ 0.08 to 0.69 $\pm$ 0.07) (Group 1). Eight of the 10 patients with abnormal LVEF responses to exercise had a decrease in LVEF >10% during exercise. The same 8 patients also had an increase in LVESVI with exercise, whereas the 5 patients with normal LVEF responses to exercise had normal or blunted LVESVI responses to exercise. Only 4 of the 10 patients with exercise-induced LV dysfunction had an angiographic LVESVI $\geq$60 ml/m^2, and only 1 had an echocardiographically determined LVESD $\geq$5.5 cm. Serial follow-up rest and exercise scintigraphic and echocardiographic measurements were made in 8 of the patients a mean of 9.4 months after the initial measurements; 3 patients were in Group 1 and 5 in Group 2. The 5 patients in Group 2 again demonstated abnormal LV function during exercise stress, and 2 of the 3 patients in Group 1 then demonstrated an abnormal LV functional response during exercise.

Therefore, it is concluded that (1) exercise radionuclide ventriculography identifies LV dysfunction earlier than traditionally used assessments, (2) LV dysfunction appears to persist in patients that demonstrate it and develop in others that did not have it originally, and (3) echocardiographic dilatation of the LVESD to 5.5 cm appears to be a late and relatively unusual occurrence.

The ideal time for aortic valve replacement in asymptomatic or mildly symptomatic patients with chronic aortic regurgitation is difficult to determine. Once symptoms develop, surgical replacement of the valve is recommended because continued medical therapy is associated with progressive clinical deterioration.[1–3] However, if surgery is delayed until the occurrence of symptoms and marked cardiomegaly, some patients have left ventricular (LV) dysfunction and do not improve symptomatically postoperatively.[4–9] Consequently, the early identification of LV dysfunction before it becomes irreversible in asymptomatic patients with chronic aortic regurgitation is a goal.

Variables used previously to identify LV dysfunction in such patients include (1) contrast angiographic

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measurement of LV ejection fraction (LVEF) <0.50 or an end-systolic volume index (LVESVI) ≥ 60 ml/m^2,[5,10] (2) M-mode echocardiographic measurement of LV end-systolic dimension (LVESD) ≥5.5 cm or LV fractional shortening ≤25%,[11,12] and (3) scintigraphic evidence at rest of an abnormal LVEF or LVESVI or an abnormal response to exercise in these variables, or both.[13,14] In this study, we tested the hypothesis that exercise radionuclide ventriculography allows earlier detection of LV dysfunction in patients with chronic aortic regurgitation than other previously described variables.

Methods

Patients: Fifteen consecutive patients (8 men, 7 women, aged 18 to 73 years, mean 44) (Table I) with chronic aortic regurgitation were evaluated with (1) cardiac catheterization and cineangiography, (2) M-mode echocardiography, and (3) rest and exercise radionuclide ventriculography. The patients were maintained on medications that the referring physician had prescribed before any objective evaluation of LV function (Table I). The average interval between catheterization and scintigraphic study was 15 days, the mean interval between scintigraphy and echocardiography was 27 days, and the mean interval between echocardiography and cardiac catheterization was 22 days. No major clinical event requiring a change in medication or hospitalization occurred in any patients during the period of these evaluations. No other cause of LV dysfunction was apparent from history or physical examination. Specifically, no patient had a history of excessive alcohol consumption, only 1 patient had a history of systemic arterial hypertension, and none had coronary arterial stenosis >50% of the luminal diameter.

LV cineangiography, supravalvular cineaortography, and intracardiac oximetry were performed in all patients to determine the presence and severity of aortic regurgitation, to exclude significant mitral valve disease, and to exclude intracardiac shunting. A coronary arterial stenosis ≥70% of the luminal diameter was considered significant. An M-mode echocardiogram was performed on a commercially available unit (Smith-Kline 20A) with the patient in the left lateral decubitus position.

The patients were exercised in the supine position on a bicycle ergometer. Electrocardiograms were monitored during rest and exercise. Graded exercise was performed beginning at either 150 or 300 kilopond meters (kpm)/min. Exercise continued with additional increments of 150 kpm every 4 minutes until 1 of the following endpoints was reached: angina, fatigue or dyspnea, 85% of the maximal age-predicted heart rate, or an S-T segment change ≥2 mm compared with the resting electrocardiogram. Blood pressure was monitored at rest and during each level of exercise.

Technique for contrast angiographic LV volume determination and quantitation of regurgitation: In each patient, a single-plane left ventriculogram in the right anterior oblique projection was performed at the time of cardiac catheterization. A lateral fluoroscopic system was used to visualize the catheter tip within the left ventricle, thus allowing accurate placement of a calibration grid with respect to the center of the ventricle. Angiographic volumes were calculated by the area-length method and corrected with use of the Kennedy regression equation.[15,16]

Forward cardiac output was determined with either the Fick or indicator dilution method. The regurgitant fraction was determined in the standard manner from angiographic and forward output measurements. Angiographic aortic regurgitation also was graded on a scale of 0 to 4+ using standard criteria.[17]

Technique for multigated equilibrium blood pool scintigraphy: Multigated equilibrium blood pool imaging was performed using a previously described technique combining both in vivo and in vitro labeling of red blood cells with 30 mCi of technetium-99m sodium pertechnetate.[18–20] Data were collected with a standard gamma scintillation camera (Ohio Nuclear Series 100, Solon, Ohio) equipped with an all purpose parallel-hole collimator and interfaced with a dedicated on line computer system (Ohio Nuclear VIP-450). At rest, equilibrium gated blood pool scintigrams were obtained in multiple projections, including a modified left anterior oblique projection, to allow the clearest separation of the left ventricle and left atrium. Supine exercise studies were gated for 32 frames per cardiac cycle and 100% of the cardiac cycle. Thereafter, each patient exercised for 1 minute at each work load before beginning a 3-minute acquisition period. Background subtraction was accomplished using a modification of the linear interpolated method described by Goris et al.[21] LVEF was determined from background corrected LV activity measured from manually constructed regions of interest placed over the end-diastolic and end-systolic frames.[22–24] The number of counts within the region of interest was used to calculate the LVEF using the following formula: (End-diastolic counts − end-systolic counts)/end-diastolic counts. This method correlates well with results obtained by contrast ventriculography.[22] An increase in LVEF of >0.05 units with maximal exercise is considered a normal functional response.[25–27]

LV volumes were determined by a nongeometric technique developed recently at our institution which is similar to methods used by others.[22–24] After background subtraction had been performed, a region of interest was constructed over the left ventricle at end-diastole and end-systole and the number of counts were determined. LV volumes were calculated from the radionuclide activity over the left ventricle normalized for the radionuclide activity per milliliter of peripheral venous blood, corrected for the acquisition time per frame, and decay of the radioisotope.[22,23] The following equation was used for scintigraphic volume calculations: (Background-corrected LV counts/[(percent cycle acquired/number of frames gated) T_{total}])/peripheral blood activity × $e^{-\lambda t}$. In this formula $e^{-\lambda t}$ is the general equation for isotope decay, $\lambda = 0.693/T^1/_2$, t = time in minutes from counting the peripheral blood sample to the midpoint of the gated study, and $T^1/_2$ for technetium-99m is 360 minutes. A decrease in LVESVI >5% with maximal exercise was considered a normal response.[13]

At our institution, LV volumes by radionuclide and contrast angiography have been shown to correlate closely.[22,23] However, in this study, we relied on the angiographic measurements of LV volumes to identify abnormalities in absolute values of LVESVI (at rest) (see Fig. 2 and 3) and have only used the scintigraphic determinations to identify exercise-induced alterations in LV volumes (Fig. 3). This was done to avoid concern about the influence of photon attenuation on the scintigraphic estimation of absolute LV volumes, which occurs especially in women with large breasts, or in patients who are extremely thin or particularly obese.

Echocardiographic technique for estimating ventricular dimensions: LV dimensions were determined at a level just below the mitral valve leaflets. The LV end-diastolic diameter (LVEDD) was measured as the vertical distance from the endocardium of the LV posterior wall to the endocardium of the ventricular septum at end-diastole measured at the time of the R wave of the electrocardiogram. Left ventricular end-systolic diameter (LVESD) was measured as the

TABLE I Clinical and Hemodynamic Data in 15 Patients With Aortic Regurgitation

Case	Age (yr) & Sex	Catheterization LVESVI (ml/m²)	RF	AR (1+ – 4+)	CAD	LVEDP (mm Hg)	Scintigraphy LVEF R	Scintigraphy LVEF EX	Echocardiography LVEDD (cm)	Echocardiography LVESD (cm)	SF	CXR CT Ratio (%)	Meds	NYHC	Symptoms
						Group 1									
1	28F	24	0.38	2+	0	13	0.67	0.72	6.0	3.8	0.37	48	0	I	0
2	18M	87	0.63	3+	0	6	0.74	0.78	5.7	3.3	0.42	59	0	II	DOE
3	23F	34	0.43	3+	0	17	0.60	0.69	5.8	3.8	0.34	50	Digoxin, diuretic	I	0
4	55M	38	0.33	3+	0	7	0.50	0.58	5.8	4.0	0.31	59	Digoxin	I	0
5	31M	32	0.45	2+	0	16	0.62	0.67	5.4	3.7	0.31	48	Diuretic	I	0
Mean	31	43	0.44	...	...	12	0.63	0.69	5.7	3.7	0.35	53	...	...	...
SD	14	25	0.11	...	...	5	0.08	0.07	0.2	0.2	0.05	6	...	...	...
p*	NS	NS	...	...	...	NS	NS	0.002	NS	NS	NS	NS	...	...	...
						Group 2									
6	44F	32	0.25	2+	50% LAD	16	0.55	0.43	4.8	3.1	0.35	45	Diuretic	I	0
7	41M	26	0.50	2+	0	14	0.66	0.57	6.2	3.8	0.39	47	0	I	0
8	32F	52	0.45	2+	0	17	0.58	0.58	6.6	4.6	0.30	54	0	II	DOE
9	47F	37	0.42	3+	0	12	0.58	0.51	6.3	4.2	0.33	53	Digoxin	I	0
10	73M	52	0.28	2+	0	24	0.71	0.58	5.0	3.2	0.36	64	Digoxin, diuretic	II	DOE
11	52M	76	0.65	4+	0	5	0.60	0.57	6.3	4.0	0.37	50	Digoxin	I	0
12	48F	41	0.58	4+	0	14	0.73	0.64	5.0	3.1	0.38	62	Digoxin, diuretic	I	0
13	23M	97	0.73	4+	0	21	0.56	0.46	7.1	5.5	0.23	62	0	II	DOE
14	72F	105	0.65	4+	0	31	0.52	0.33	6.8	3.6	0.47	73	Digoxin, diuretic	I	0
15	65M	177	0.61	3+	0	19	0.35	0.29	6.3	4.9	0.22	62	Digoxin, diuretic	II	DOE
Mean	50	70	0.51	...	...	17	0.58	0.50	6.0	4.0	0.34	57	...	...	...
SD	16	46	0.16	...	...	7	0.11	0.12	0.8	0.8	0.07	9	...	...	...

* p values represent comparison of parameters in Group 1 versus Group 2.

AR = aortic regurgitation; CAD = coronary artery disease; CT ratio = cardiothoracic ratio; CXR = chest x-ray; DOE = dyspnea on exertion; Ex = exercise; LAD = left anterior descending; LVEDD = left ventricular end-diastolic dimension; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESVI = left ventricular end-systolic volume index; Meds = medications; NS = not significant; NYHC = New York Heart Association functional class; R = rest; RF = regurgitant fraction; SF = shortening fraction; 0 = absent.

vertical distance from the endocardium of the LV posterior wall at the peak of its anterior motion during systole to the endocardium of the ventricular septum at its maximal downward deflection during systole. The percent change in minor diameter or shortening fraction was calculated by the following equation: (LVEDD − LVESD)/LVEDD.

Results

The clinical and hemodynamic data in the 15 patients comprising this study are shown in Table I. Exercise radionuclide ventriculography identified 2 groups of patients (Fig. 1). Group 1 (5 patients) had a LVEF ≥0.50 and a normal LVEF response to peak exercise (that is, an increase in LVEF ≥0.05 units at peak exercise compared with the supine resting LVEF (0.63 ± 0.09 to 0.69 ± 0.07) (Fig. 1) and no change or a decrease in LVESVI with exercise (Fig. 2). Group 2 (10 patients) failed to have an increase in LVEF at peak exercise from the resting value (0.58 ± 0.11 to 0.50 ± 0.12); in 8 of the 10 patients LVEF decreased 10% from the resting LVEF value at peak exercise (Fig. 1). The degree of aortic regurgitation was similar in these 2 groups (regurgitant fraction 0.44 ± 0.11 versus 0.51 ± 0.16; p = NS [not significant]. Patients in Group 2 also demonstrated a marked increase in LVESVI at peak exercise (Fig. 3). LVESVI at rest (by contrast angiography) as well as the calculated absolute LVESVI at peak exercise (calculated by multiplying the absolute contrast angiographic values at rest by the percent change during exercise as determined scintigraphically) are shown for both groups in Figure 2. The relation between the percent increase in LVESVI at peak exercise (determined scintigraphically) and the LVESVI at rest (determined by contrast angiography) for patients in both groups is shown in Figure 4.

The heart rate, blood pressure, and work load data for both groups of patients are shown in Table II. Although the maximal heart rate, rate-pressure double product, and work load achieved were somewhat lower in patients in Group 2, this difference was not significant statistically.

Angiographic volumes: LVESVI at rest by contrast angiography is shown in Table I. One patient in Group 1 and 4 patients in Group 2 had an LVESVI ≥60 ml/m^2. Four of 5 patients with angiographic LVESVI ≥60

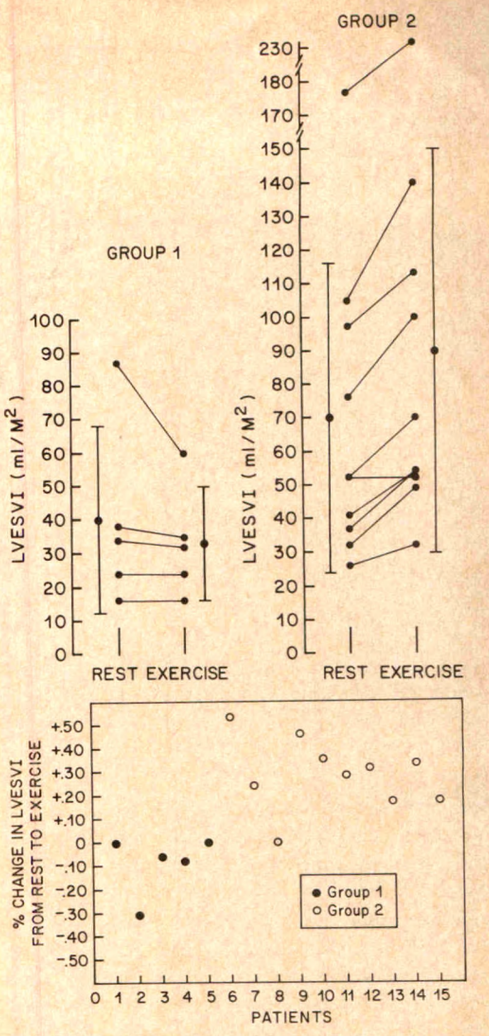

FIGURE 2. Top, left ventricular end-systolic volume index (LVESVI) at rest (by contrast angiography) and the calculated absolute LVESVI at peak exercise (calculated by multiplying absolute contrast angiographic values at rest by percent change during exercise as determined scintigraphically) for patients in Groups 1 and 2. Means ± 1 standard deviation are shown. **Bottom,** percent change in LVESVI from rest to peak exercise determined scintigraphically for each of the 15 patients studied. **Solid circles** indicate patients in Group 1, **open circles** patients in Group 2.

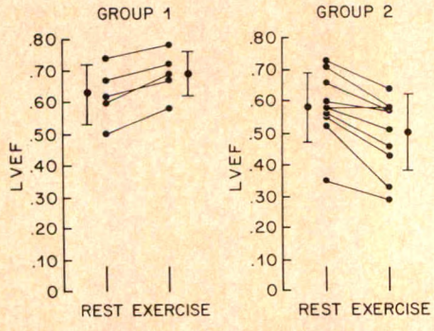

FIGURE 1. Scintigraphically determined left ventricular ejection fractions (LVEF) at rest and peak exercise. The exercise responses identified 2 groups of patients. Group 1 had a normal LVEF response and Group 2 had an abnormal LVEF response. Each line represents the data from 1 patient, and the mean ±1 standard deviation of each group at rest and exercise is shown.

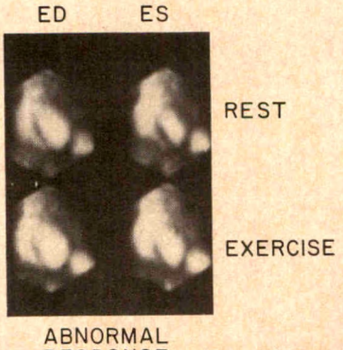

FIGURE 3. Modified left anterior oblique projection of end-diastolic (ED) and end-systolic (ES) images at rest and peak exercise. Note the increase in end-systolic image at peak exercise.

TABLE II Hemodynamic Data

Case	HR (beats/min)		SBP (mm Hg)		Work Load (kpm/min)	Rate-Pressure Product × 10^2	
	Rest	Ex	Rest	Ex		Rest	Ex
				Group 1			
1	71	106	125	150	300	89	159
2	58	135	135	190	600	78	257
3	60	150	140	180	450	84	270
4	100	150	160	180	150	160	270
5	75	94	125	150	300	94	141
Mean	73	127	137	170	360	101	219
SD	17	26	14	19	171	34	64
p*	NS	NS	NS	NS	NS	NS	NS
				Group 2			
6	60	107	170	190	300	102	203
7	52	107	140	200	450	73	214
8	55	105	140	160	300	77	168
9	65	117	140	230	150	91	269
10	75	105	170	190	150	128	200
11	72	94	165	235	300	119	221
12	75	88	160	160	150	120	141
13	47	100	130	160	300	61	160
14	88	100	170	220	150	150	220
15	48	94	120	170	300	58	160
Mean	64	102	151	192	255	98	196
SD	14	8	19	29	101	31	38

* p values represent comparison of parameters in Group 1 versus Group 2.
Ex = exercise; HR = heart rate; SBP = systolic blood pressure; SD = standard deviation.

ml/m^2 had abnormal LV function responses to exercise. However, 6 of 10 patients with LVESVI ≤60 ml/m^2 also had abnormal LV responses to exercise.

M-mode echocardiography: The M-mode echocardiographic measurements are shown in Table I. All patients in Group 1 had normal LVESD (3.7 ± 0.2 cm). One patient in Group 2 had a LVESD ≥5.5 cm and 2 patients had LV shortening fractions ≤25.

Cardiothoracic ratios: The cardiothoracic ratio determined from standard posteroanterior chest roentgenograms are shown in Table I. The cardiothoracic ratios in both Groups 1 and 2 varied widely. Group 1 (normal response to exercise) had a range of 0.48 to 0.59 and a mean of 0.53 ± 0.06. Group 2 (abnormal response to exercise) had a range of 0.45 to 0.73 and a mean of 0.57 ± 0.09. Three patients in Group 2 (Patients 6, 7, and 10) had normal cardiothoracic ratios despite demonstrating global LV dysfunction with exercise, whereas 2 patients in Group 1 (Patients 2 and 4) demonstrating a normal response to exercise had an abnormal cardiothoracic ratio (>0.50).

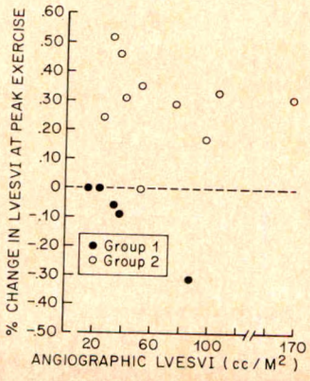

FIGURE 4. Percent change in left ventricular end-systolic volume index (LVESVI) versus the resting angiographic LVESVI for each patient.

Follow-up data: Eight patients underwent serial evaluation with rest and exercise radionuclide ventriculograms and M-mode echocardiograms during a mean follow-up period of 9.4 months (range 4 to 23 months) (Tables III and IV). All patients were asymptomatic at the time of the repeat studies. No major clinical event requiring a change in medication or hospitalization occurred in any of these patients during this period.

Three patients were in Group 1 and 5 were in Group 2. All 5 patients in Group 2 again demonstrated an abnormal response to exercise with a decrease in LVEF at peak exercise (0.64 ± 0.06 to 0.56 ± 0.07, mean ± SD), as well as an increase or no change in LVESVI (mean increase 28%) (Fig. 5). Two patients in Group 1 (Fig. 5) (Patients 1 and 4) who originally demonstrated a normal response to exercise demonstrated a marked decrease in LVEF at peak exercise (0.54 ± 0.07 to 0.44 ± 0.13) during the follow-up study. One patient (Patient 3) (Fig. 6) again showed a normal LVEF response to exercise. All 3 patients showed an abnormal LVESVI response to exercise.

The echocardiographic LVESD did not change significantly in patients in Group 2 from the original to the follow-up study (3.8 ± 0.7 to 3.6 ± 0.7) (Table III). The 2 patients in Group 1 who demonstrated an abnormal exercise LVEF response on repeat study both had an increase in LVESD (Table III), but no patient in either group who had an abnormal response to exercise during

TABLE III Follow-Up Scintigraphic and Echocardiographic Data

Case	Follow-Up (mo)	Scintigraphy 1 LVEF		Scintigraphy 2 LVEF		Echo 1		Echo 2	
		R	Ex	R	Ex	LVEDD (cm)	LVESD (cm)	LVEDD (cm)	LVESD (cm)
					Group 1				
1	23	0.67	0.72	0.59	0.53	6.0	3.8	6.6	4.5
3	5	0.60	0.69	0.59	0.64	5.8	3.8	5.5	3.5
4	7	0.50	0.58	0.49	0.35	5.8	4.0	6.5	4.8
Mean	12	0.59	0.66	0.56	0.51	5.9	3.9	6.2	4.2
SD	10	0.09	0.07	0.06	0.15	0.1	0.1	0.6	0.7
					Group 2				
6	5	0.55	0.43	0.67	0.57	4.8	3.1	4.4	2.8
7	8	0.66	0.57	0.65	0.64	6.2	3.8	5.6	3.8
8	5	0.58	0.58	0.59	0.50	6.6	4.6	5.7	4.4
9	18	0.58	0.51	0.57	0.49	6.3	4.2	5.9	4.0
12	4	0.73	0.64	0.72	0.62	5.0	3.1	4.8	3.1
Mean	8	0.62	0.55	0.64	0.56	5.8	3.8	5.3	3.6
SD	6	0.07	0.08	0.06	0.07	0.8	0.7	0.6	0.7

Echo = Echocardiography; other abbreviations as in Table I.

TABLE IV Hemodynamic Data on Follow-Up Rest and Exercise Scintigraphy

Case	HR (beats/min)		SBP (mm Hg)		Work Load (kpm/min)	Rate-Pressure Product × 10^2	
	Rest	Ex	Rest	Ex		Rest	Ex
				Group 1			
1	83	125	150	180	300	124	225
3	65	115	130	160	300	85	184
4	80	115	160	190	300	128	218
Mean	76	118	147	177	300	112	209
SD	10	6	15	15	0	24	22
				Group 2			
6	75	125	150	200	300	113	250
7	60	107	160	180	300	96	193
8	71	88	122	150	150	87	132
9	62	136	180	250	300	112	340
12	75	94	150	160	150	113	150
Mean	69	110	152	188	240	104	213
SD	7	20	21	40	82	12	75

Abbreviations as in Table II.

the repeat evaluation had a LVESD ≥5.5 cm or an LV shortening fraction ≤25%.

Discussion

In patients with aortic regurgitation, it is generally agreed that valve replacement should be performed before irreversible LV dysfunction occurs.[28] In this condition, symptoms may not appear despite marked cardiac enlargement and the presence of LV dysfunction. However, once preoperative LV dysfunction is present, postoperative survival is reduced.[5] Therefore, various methods have been used to detect early LV dysfunction in patients with hemodynamically important aortic regurgitation who may be asymptomatic or only mildly symptomatic in an attempt at preempting the onset of irreversible LV dysfunction and its sequelae.

Earlier investigators have measured the pulmonary capillary wedge pressure, cardiac output, LV end-diastolic pressure, and LV end-diastolic volume in patients with aortic regurgitation. However, increases in the pulmonary capillary wedge pressure and decreases in the cardiac output occur relatively late in these patients.[29] In addition, the pulmonary capillary wedge pressure and cardiac output, LV end-diastolic pressure, and LV end-diastolic volume do not necessarily reflect LV contractile function directly, because they are dependent on LV compliance, the degree of valvular regurgitation, heart rate, and volume status.[30,31]

Forman et al[5] found that a preoperative LVEF <0.50 was associated with a poorer 3-year postoperative survival than a preoperative LVEF >0.50 (64 versus 93%). These findings have been corroborated by other investigators.[32,33]

However, the ejection fraction is preload-dependent, and variable alterations of blood pressure, venous return, heart rate, and circulating catecholamines combined with alterations in impedance to LV emptying

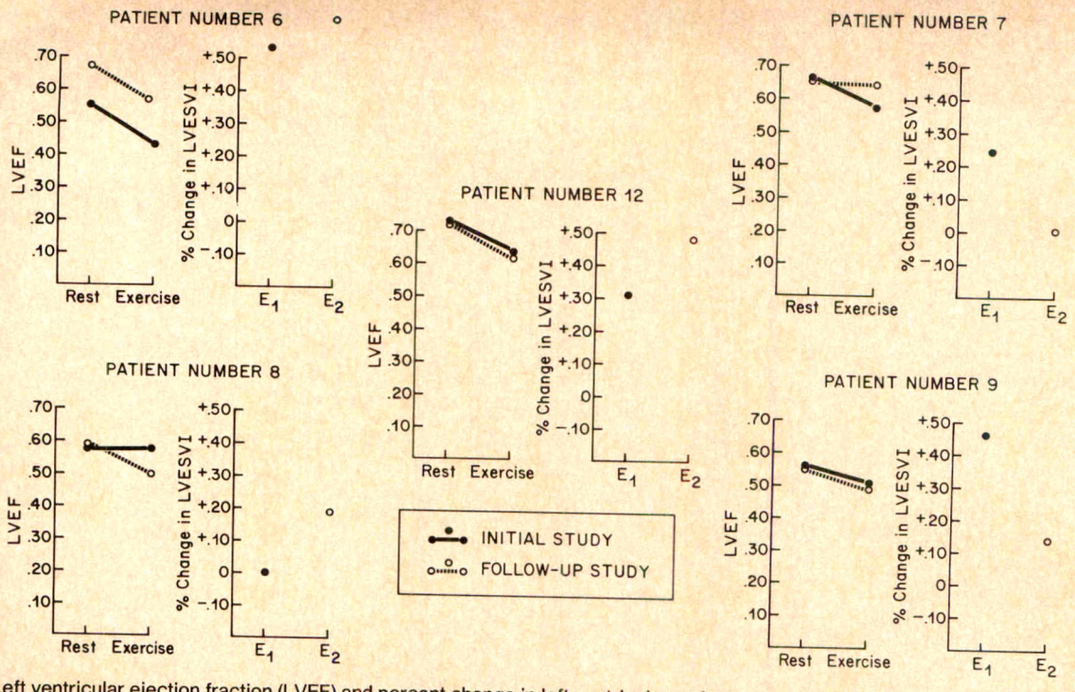

FIGURE 5. Left ventricular ejection fraction (LVEF) and percent change in left ventricular end-systolic volume index (LVESVI) at rest and exercise as determined scintigraphically in the 5 patients in Group 2 who underwent serial studies. **Solid lines** or **solid circles** indicate original study; **dotted lines** or **open circles** represent follow-up study. All 5 patients again demonstrated an abnormal response to exercise in the follow-up study. E_1 = original exercise response; E_2 = exercise response on follow-up study.

make LVEF a less than perfect means to characterize LV function at rest or exercise in patients with hemodynamically important aortic regurgitation.[13,34]

For example, if tachycardia predominates during exercise, a decrease in ejection fraction may be the result of a change in preload rather than deterioration in LV performance. An increase in arterial pressure may cause LV end-diastolic volume to increase, but ejection fraction to decrease or not change.

Data suggest that end-systolic fiber length closely reflects the contractile state of the ventricular myocardium and is preload-independent.[35–37] Because end-systolic volume is linearly related to the pressure at end-systole,[35] it would seem to provide a valuable assessment of myocardial function, and because it is relatively preload-independent, it should be especially helpful in patients with altered preload from LV volume overload.[10] Therefore, the end-systolic volume may provide a better assessment of LV performance than previously described variables including ejection fraction. Borow et al[10] found that an increased preoperative LVESVI ($\geq$60 ml/m^2) by contrast angiography correlated with postoperative LV dysfunction and increased perioperative mortality in these patients. However, serial contrast angiographic assessments of LV volumes cannot be performed easily, are invasive, and may be inaccurate when LV geometry is distorted. Radionuclide ventriculography provides an alternative method of assessing LV function because it is noninvasive, can be used serially, and can be applied during exercise. In addition, we and others have demonstrated that accurate LV volume determinations can be made independent of geometric assumptions concerning LV shape.[22–24]

Henry et al[11,12] emphasized that patients with an M-mode echocardiographically determined LVESD $\geq$5.5 cm or an LV shortening fraction $\leq$25% have a high operative and postoperative mortality. Thus, they recommended surgical intervention in asymptomatic subjects before the development of these alterations. However, echocardiographic assessment may be technically difficult, especially in patients with dilated left ventricles. In addition, errors in reproducibility are inherent in serial determinations and measurements.[7,38–41] Furthermore, it is not clear whether this degree of LV dilatation occurs before, concomitant with, or after other evidence of LV dysfunction.

Borer et al[25] and Dehmer et al[13] have shown that asymptomatic patients with chronic aortic regurgitation may have a "normal" LVEF at rest, but that it may decrease with exercise. Dehmer et al also demonstrated that some patients with aortic regurgitation have an abnormal increase in LVESVI with exercise, even though the LVEF is normal at rest.

In the present study, we found that 10 of 15 consecutive, asymptomatic (or mildly symptomatic) patients with aortic regurgitation demonstrated LV dysfunction, as evidenced by a failure to increase LVEF or decrease LVESVI with peak exercise. Despite scintigraphic evidence of LV dysfunction during exercise stress in these 10 patients, only 4 had angiographic LVESVI $\geq$60 ml/m^2, and only 1 had an echocardiographically determined LVESD $\geq$5.5 cm. Moreover, only 2 patients had an LV shortening fraction $\leq$25%. Lewis et al[42] also

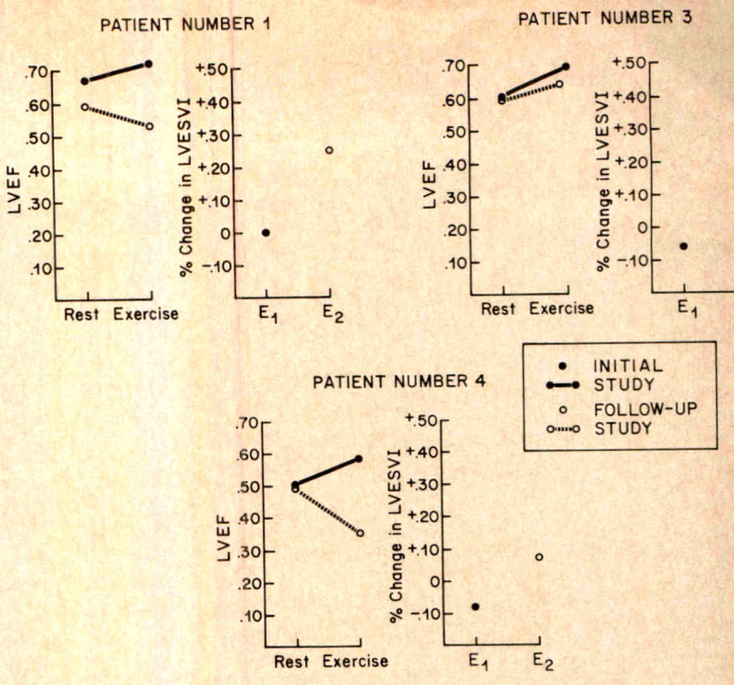

FIGURE 6. Left ventricular ejection fraction (LVEF) and percent change in left ventricular end-systolic volume index (LVESVI) at rest and exercise as determined scintigraphically in serial studies in 3 patients in Group 1. Two of 3 patients who originally demonstrated a normal response to exercise demonstrated a decrease in LVEF and an increase in LVESVI during the follow-up study. Abbreviations as in Figure 5.

found that a failure to increase or an absolute decrease in LVEF with exercise occurs before increases in LV end-systolic diameter determined echocardiographically in a study of 45 patients with chronic aortic regurgitation. However, in the study of Lewis et al, only 18 of 45 patients underwent cardiac catheterization and LV volumes were not measured scintigraphically. Because LVEF responses are dependent on preload and heart rate, the failure to analyze another (and probably better) variable to characterize LV systolic function, that is, the LVESVI at rest and exercise, leaves one uncertain as to whether LV dysfunction actually occurred. However, the study of Lewis et al and the present one taken together suggest that LV global dysfunction often exists before marked dilatation of the LV as detected by angiographic or echocardiographic measurement.

Recently, Schuler et al[43] studied 14 asymptomatic patients with isolated aortic regurgitation and found that the end-systolic pressure-volume relation identified 2 subsets of asymptomatic patients, 1 with impaired myocardial contractility and normal LV exercise reserve and a second with depressed myocardial contractility and LV dysfunction during exercise. In the present study, serial rest and exercise radionuclide ventriculograms demonstrated that the abnormal response to peak exercise was reproducible. In addition, we found evidence of LV dysfunction at peak exercise (as demonstrated by a decrease in LVEF and an increase in LVESVI at peak exercise) in 2 of 3 patients who showed a normal response to exercise originally. All patients who underwent serial analysis and demonstrated an abnormal response to exercise initially continued to have a normal LVESD on M-mode echocardiography.

Although the number of patients studied in the present evaluation is relatively small and validation of these results in a larger number of patients is necessary, our findings demonstrate (1) exercise radionuclide ventriculography identifies LV dysfunction earlier than previously described variables and before the onset of symptoms; (2) echocardiographic dilatation of the LVESD to ≥5.5 cm and LV fractional shortening ≤25% appear to be late, unusual occurrences; and (3) serial analysis with rest and exercise radionuclide ventriculography provides a valuable method of following up patients with chronic aortic regurgitation and for detecting early LV dysfunction.

Whether the ability to identify early LV dysfunction during exercise will influence the decision relative to when to intervene in asymptomatic patients with chronic aortic regurgitation is uncertain. However, this study should provide the basis for further prospective evaluations to assess the consequence of various forms of treatment of asymptomatic patients with chronic aortic regurgitation and exercise-induced LV dysfunction.

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Effect of Elevating the Wrist on the Radial Pulse in Aortic Regurgitation: Corrigan Revisited

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Five patients with severe aortic regurgitation had their intraarterial radial pulse recorded simultaneously with the external radial artery deflection of the other wrist. Recordings were made with the arms horizontal and repeated after elevation of the wrists, until the arms were vertical. Elevating the arm of a patient with aortic regurgitation increased the pulsation recorded over the radial artery, lowered mean intraarterial pressure, and reduced the pulse pressure. The results suggest that elevation increases the compliance of the arterial wall, primarily by moving the artery to a lower position on its pressure-volume curve. The same changes occurred in 5 normal subjects but were less pronounced.

The increased pulsation of the radial artery that is felt in patients with aortic regurgitation (AR) becomes more noticeable when the wrist is raised. The effect was first described by Corrigan,[1] whose patient would "increase the pulsation of the brachial and palmar arteries to a most striking degree by elevating his arms to a perpendicular position above his head." Although this effect is accepted, the standard cardiologic and medical textbooks offer no satisfactory explanation. Corrigan believed that elevation makes the arteries "more flaccid" and "their visible pulsation of course more marked." Friedberg[2] thought elevation enhanced the pulse because "the radial artery is then in more direct line with the outflow stream from the aorta, and because gravity increases blood pressure changes at the wrist." This study records changes in arterial excursion and intraarterial pressure produced by elevation, and offers an explanation for the effect.

Methods

Subjects: Ten subjects were studied: (5 normal control subjects and 5 patients with at least grade 3/4 AR assessed angiographically). The age of the control subjects ranged from 26 to 60 years (mean 46) and of those with AR from 42 to 73 years (mean 55).

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The subjects were studied lying in the supine position. The pickup used to record the pulse over the radial artery was a flat cup (2 cm in diameter and 0.5 cm deep), which was held in position by adhesive tape and by a sprung clamp that applied pressure to the top of the cup and to the underside of the wrist only. The cup was connected by a 12 cm tube to a Cambridge piezoelectric pulse transducer taped to the forearm, and then to a Cambridge multichannel recorder. The recorder was set with the same sensitivity for each study, and the position of the cup adjusted before the start to obtain the maximum deflection possible.

To measure intraarterial pressure, a short 20G cannula was inserted into the other radial artery and connected to a Hewlett-Packard transducer and 7745B multichannel re-

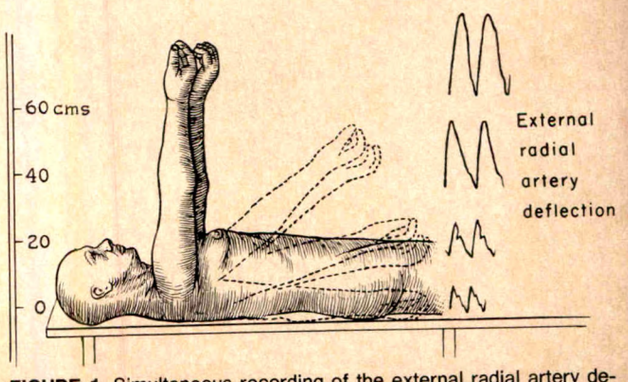

FIGURE 1. Simultaneous recording of the external radial artery deflection of 1 wrist and the intraarterial pressure of the other. Recordings were taken at rest (0), 20, 40, and 60 cm above 0. At 60 cm the arms were vertical. The deflections drawn are not actual size.

corder. Before each pressure measurement the gauge was set to the height of the wrist.

The subjects' arms were rested at their sides and the intraarterial pressure and the external pulse were recorded simultaneously, and marked position 0. With the arms kept extended, the wrists were then raised to 20, 40, and 60 cm above this level and recordings taken in each position (Fig. 1). The last position resulted in the arms being almost vertical. The subject was then asked to return the arms to the resting position when repeat recordings were taken.

TABLE I Results

Case Age (yr)	Arm Position (cm)	Deflection	BP (mm Hg)	Mean BP (mm Hg)	D/D_0
		Normal Subjects			
	0	2.0	155/85	108	1.0
1	20	2.4	120/62	83	1.2
	40	3.1	118/55	75	1.6
(60)	60	4.1	102/38	62	2.1
	0	2.0	132/73	95	1.0
	0	2.5	180/100	125	1.0
2	20	2.6	170/95	120	1.0
	40	2.8	140/65	100	1.1
(50)	60	3.8	130/60	85	1.5
	0	2.3	180/100	125	0.9
	0	0.8	175/95	125	1.0
3	20	0.9	150/85	110	1.1
	40	1.0	130/70	100	1.2
(50)	60	1.6	110/50	75	2.0
	0	0.8	170/100	125	1.0
	0	1.2	157/90	110	1.0
4	20	2.1	137/79	95	1.8
	40	2.1	118/62	80	1.8
(50)	60	2.4	107/48	65	2.0
	0	1.3	147/92	105	1.1
	0	0.9	160/98	115	1.0
5	20	1.1	148/93	110	1.2
	40	1.6	118/65	80	1.8
(38)	60	1.6	103/51	70	1.8
	0	0.9	166/108	118	1.0
		Patients With Aortic Regurgitation			
	0	2.2	210/50	85	1.0
6	20	3.2	165/45	73	1.4
	40	5.6	155/29	60	2.5
(73)	60	6.8	145/15	50	3.1
	0	1.7	197/53	83	0.8
	0	1.2	149/66	85	1.0
7	20	3.1	132/55	73	2.6
	40	3.7	104/40	57	3.1
(42)	60	5.5	82/25	37	4.6
	0	1.4	157/76	105	1.2
	0	3.1	234/50	90	1.0
8	20	3.5	200/35	75	1.1
	40	7.2	193/22	65	2.3
(63)	60	9.6	183/6	50	3.1
	0	3.8	250/50	90	1.2
	0	1.2	210/80	115	1.0
9	20	1.6	190/55	95	1.3
	40	2.2	190/40	80	1.8
(65)	60	2.8	180/30	70	2.3
	0	1.2	220/75	115	1.0
	0	1.5	240/95	123	1.0
10	20	2.3	200/75	105	1.5
	40	2.9	175/50	85	1.9
(45)	60	4.0	145/35	65	2.7
	0	1.5	220/90	120	1.0

BP = blood pressure; D = deflection (cm) of the radial artery pulse with the wrist elevated; D_0 = deflection (cm) of the radial artery pulse at rest or 0 position.

Results

The results are summarized in Table I. In every control subject and in every patient with AR, the radial arterial deflection increased with each elevation of the wrist, and reached a maximum when the arm was in a vertical position. In patients with AR, the increase in deflection with the wrist elevated was greater than in the normal subjects (Fig. 2). The increasing deflection was always associated with a decrease in mean blood pressure. In the normal subjects mean blood pressure decreased progressively from an average of 117 mm Hg with the wrist at rest to 71 mm Hg when the wrist was elevated to 60 cm. In those with AR, mean pressure decreased from an average of 100 mm Hg at rest to 54 mm Hg when vertical.

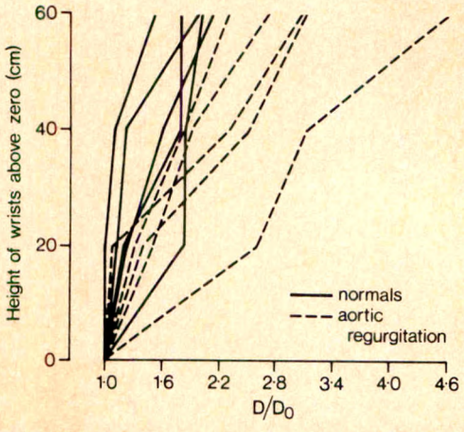

FIGURE 2. Effect of raising the arm on the pulsation of the radial artery. D = excursion of the pulse when the arm is raised; D_0 = excursion of the pulse when the arm is horizontal.

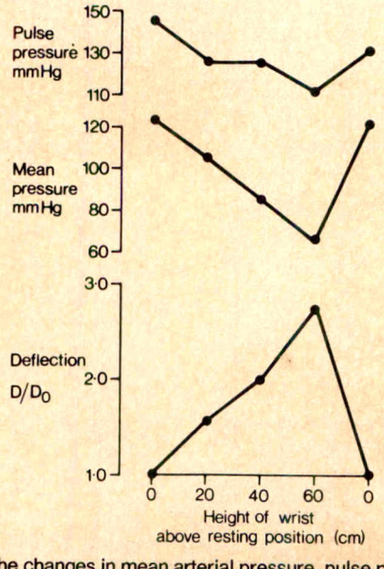

FIGURE 3. The changes in mean arterial pressure, pulse pressure, and arterial deflection of the radial artery that accompanied raising the arm in a patient with aortic incompetence. D = excursion of the pulse when the arm is raised; D_0 = excursion of the pulse when the arm is horizontal.

The pulse pressure also was reduced with elevation. In the normal subjects, pulse pressure decreased from an average of 70 mm Hg in the resting position to 61 mm Hg in the vertical position. In those with AR, it decreased from an average of 140 to 125 mm Hg. The changes in pressure and arterial deflection of 1 patient with AR (Case 6) are shown as an example in Figure 3.

Discussion

No attempt was made to compare the external pulse of 1 patient with that in another, because the pulse in each depends on the relative position of the cup and the artery. However, once the cup is clamped to the artery, the pulses recorded in the elevated position (D) may be compared with those at rest (D_0). Our results showed that D/D_0 increased with each elevation of the wrist.

A piezoelectric crystal may respond to rate of change rather than magnitude of the deforming signal, and the rate of change of blood pressure (dp/dt) increases when patients with AR stand erect.[3] The time constant of the crystal was 1.9 seconds, which suggested that its response to rate of change was minimal.[4] To be certain, we repeated 1 study, using an air-filled pickup with a strain gauge that measured only magnitude of arterial excursion. This produced identical tracings, and the pulse increased in exactly the same way when the wrist was elevated. Alterations in pulse rate also affect the dp/dt within the artery, but our control subjects showed only slight increase in pulse rate with elevation, and those with AR showed no change. Thus the changes produced by elevation were an increased external pulse, a lowered mean pressure, and a narrowed pulse pressure. The changes, taken together, suggest that elevation increases the compliance of the arterial wall. Previous studies have shown the pressure-volume relationship of arteries to be curvilinear.[5] It is because of this that in the presence of a lower mean pressure the vessel becomes more compliant, and therefore has a greater excursion (and hence deflection) with each pulse.

If this is true the same effect should be evident in other arteries. Corrigan noted that a bounding pulse in the leg became more noticeable when the foot was raised. One patient with AR also was studied using the dorsalis pedis artery. With the leg horizontal the arterial deflection was 3.1 cm and increased to 8.6 cm in the elevated position. Corresponding pressures were 220/65 mm Hg (mean 95) and 130/25 mm Hg (mean 50). Elevation, therefore, affects legs and arms in the same way.

Thus our observations agree with those of Corrigan, as does our interpretation. Elevation of the legs and arms increases the arterial compliance or, in his words, "makes the artery more flaccid."

Acknowledgment: We thank John Norman for his invaluable assistance and technical advice.

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Effects of Disopyramide on Left Ventricular Function: Assessment by Radionuclide Cineangiography

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To determine the effects of disopyramide on resting systolic left ventricular (LV) function and LV functional reserve, gated equilibrium radionuclide cineangiography was performed at rest and during maximal symptom-limited supine bicycle exercise in 12 patients after a single 300 mg oral loading dose of disopyramide, and in 22 patients (including the 12 patients just mentioned) after they received disopyramide 150 mg 4 times daily for 5 to 10 days (average 7). The oral loading dose (average serum level 3.6 ± 1.3 μg/ml [standard deviation]) produced decreases in ejection fraction in 9 of 12 patients with a decrease in average resting ejection fraction from 40 ± 15% to 33 ± 11% ($p < 0.005$). However, the lower, sustained dosage of disopyramide was associated with a lower average serum level of 2.5 ± 0.8 μg/ml and with smaller but significant decreases in ejection fraction in 3 of 22 patients during exercise only. At this dosage there was no significant decrease in average ejection fraction for the group at rest or during exercise. Adverse effects of disopyramide on ejection fraction occurred even in patients with previously normal LV function at rest. Hence, disopyramide may be associated with significant decreases in LV systolic function, particularly when given in high, oral "loading" doses. However, sustained therapy with lower dosages as well as lower drug levels is also associated with less depression of LV function.

Disopyramide phosphate (Norpace®) is a relatively recently introduced antiarrhythmic drug[1] with therapeutic efficacy[2–4] in the treatment of supraventricular and ventricular arrhythmias. The cardiac effects of disopyramide resemble those of quinidine in that both drugs reduce the rate of increase and amplitude of the cardiac muscle action potential and decrease automaticity. Unlike quinidine, depression of left ventricular (LV) function[5–9] has been considered a substantial difficulty. Although congestive heart failure was initially noted in patients with renal failure or previous cardiac decompensation or after large loading doses of a drug, a more recent clinical study suggests a high frequency of congestive heart failure even in patients with intact renal function.[9] To determine resting systolic LV function and LV functional reserve, gated equilibrium radionuclide cineangiography was performed at rest and during exercise before and after the administration of an oral loading dose, and during sustained therapy with disopyramide.

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Methods

Patients: Patients with coronary artery disease and idiopathic dilated cardiomyopathy receiving antiarrhythmic drugs for suppression of ventricular ectopic beats were studied. The group consisted of 22 men with an average age of 60 years (range 44 to 80). Seventeen patients had coronary heart disease documented by coronary angiography (10 patients) or by previous documentation of acute myocardial infarction (7 patients). Five patients had idiopathic dilated cardiomyopathy; all were habitual alcoholics. In 3, coronary angiography disclosed <50% diameter reduction in any coronary artery; 2 patients had LV dysfunction without a previous history of acute myocardial infarction or angina pectoris. In addition, they did not have abnormal Q waves on electrocardiogram or

regional wall motion abnormality on radionuclide cineangiogram. Twelve patients were taking digitalis and 17 diuretics, although none had uncontrolled congestive heart failure at study.

Long-acting nitrates were discontinued at least 10 hours and quinidine or procainamide at least 1 week before study. Radionuclide angiography was performed at baseline and an average of 7 days (range 5 to 10) after beginning disopyramide 150 mg 4 times daily. On this sustained therapeutic regimen, radionuclide imaging was performed 2 to 3 hours after the last dose, at which time blood was drawn for measurement of the disopyramide level. In the first 12 patients studied, radionuclide cineangiography also was performed 2 hours after the ingestion of disopyramide administered as an acute oral loading dose of 300 mg, before beginning sustained therapy. Determination of ejection fraction at rest and during exercise in these 12 patients was performed at baseline just before the administration of disopyramide. Venous blood for measurement of serum levels of disopyramide was drawn 90 minutes after the 300 mg oral loading dose just before repeat imaging. Disopyramide levels were measured[10] by high-pressure liquid chromatography.

To exclude the possible effects of repeated exercise testing or other factors on multiple determinations of ejection fraction performed within a short time, an additional 10 patients (8 with coronary artery disease and 2 with aortic regurgitation) underwent 2 rest-exercise sequences, separated by 45 to 60 minutes, without intervening drug therapy.

Radionuclide cineangiography: Radionuclide cineangiography was performed with the subjects in a supine position at rest and during maximum symptom-limited supine bicycle exercise.[11] In vivo labeling of red blood cells with 25 mCi of technetium-99m was effected by injecting the isotope a half hour after the intravenous administration of stannous pyrophosphate. This dose of technetium coupled with a high sensitivity collimator results in 200,000 counts/frame in a 15 × 15 cm field surrounding the heart. After equilibration of the tracer in the blood pool, an Anger camera was oriented in the modified left anterior oblique position to isolate the left ventricle in the field of view.[12] Imaging was performed with a computer-based procedure gated to the electrocardiogram. LV ejection fraction could then be determined by computer-assisted analysis of LV time activity curves, using a commercially available system (General Electric, Med IV), and software (Medical Data Systems, MUGE). With this system, data were stored on a 12-sector disc and transferred to a minicomputer in real time. The initial 80% of the cardiac cycle, beginning at end-diastole, is divided into 14 equal frames, each with a spatial resolution of 64 × 64 pixels. At resting heart rates, ranging in our patients from 53 to 107 beats/min, this frame rate produced a temporal resolution of 0.06 second at the lowest resting heart rate observed and 0.03 second at the highest. Temporal resolution was 0.05 second or better in 52 of 56 studies performed at rest and in all 56 studies performed during exercise. Acquisition of data at rest over 5 to 8 minutes resulted in approximately 9,000 to 15,000 counts within the LV border at end-diastole. The LV border was determined by computer within a rectangle placed by the operator around the LV region of interest. The algorithm used identifies the LV border on a frame-by-frame basis, using both threshold and second derivative criteria. Each frame was reviewed by the operator. Appropriate changes in the count threshold were made as necessary, so that the final LV region of interest conformed to the visual image. Background was selected by the computer 5 pixel-widths from the inferolateral aspect of the LV border. The background-corrected LV time-activity curve was plotted on hard copy. Ejection fraction was determined automatically from the counts at the end-diastolic frame, determined at the peak of the curve, and from counts at the end-systolic frame, determined at the nadir of the curve. Excellent correspondence ($r = 0.90$, $p < 0.001$, $n = 32$) of radionuclide ejection fraction with those obtained by contrast angiography has previously been established in this laboratory. The ejection fraction in this comparison ranged from 10 to 87% (49 ± 29%, mean ± standard deviation [SD]) on contrast angiography and ranged from 13 to 69% (mean 40 ± 15%) on radionuclide cineangiography. The interstudy variability of ejection fraction in our laboratory, determined in 20 stable patients over several days, is 3 ± 2% (average ± SD ejection fraction units) with a range of 0 to 6%.

After images were obtained at rest, supine bicycle exercise was begun with 100 kpm-m increments in exercise load at 2-minute intervals. Exercise was continued until limitation by severe failure, chest pain, or severe dyspnea. Imaging was begun when the patient indicated severe fatigue and was continued an additional 2 or 3 minutes as required for acquisition of statistically sufficient data. Ejection fraction was calculated using the methods described herein. In all subjects, heart rate and blood pressure (measured using arm cuff sphygmomanometry) were recorded at 1- to 2-minute intervals during exercise.

Data are presented as the mean ± SD. Changes in ejection fraction are expressed as absolute values. A decrease in ejection fraction from 60 to 45% is a 15% change. A change in ejection fraction of >7% (interstudy variability mean ± 2 SD) was considered to represent a significant change in an individual patient. Comparisons of means between baseline ejection fractions and those determined after disopyramide were made using Student's t test for paired data. The criterion of significance was $p < 0.05$.

Results

An oral loading dose of disopyramide 300 mg (average serum level 3.6 ± 1.3 μg/ml, range 2.0 to 5.9) was associated with significant decreases (Fig. 1) in ejection fraction in 9 of 12 patients, either at rest only (3 patients), with exercise only (3 patients), or during both rest and exercise (3 patients). Decreases in ejection fraction from baseline values were as great as 18% at rest and during exercise. In addition, after disopyramide the average ejection fraction at rest for the group of 40 ±

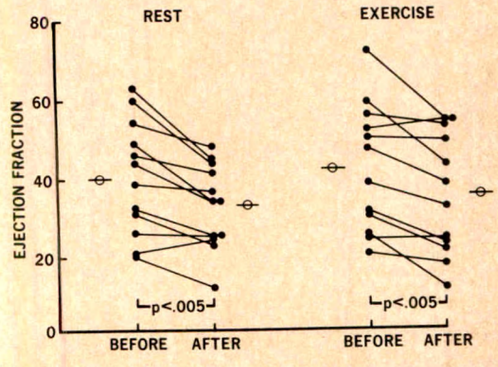

FIGURE 1. Response of resting (**left panel**) and exercise (**right panel**) ejection fraction to single 300 mg oral dose of disopyramide. Decreases of ejection fraction up to 18% at rest or during exercise, or both, are noted in most patients (9 of 12). The decrease in average ejection fraction at rest or with exercise is significant. Note that even 3 patients with previously normal ejection fractions (49, 60, and 63%) show decreases after disopyramide (**left panel**).

TABLE I Hemodynamic Effects of Disopyramide at Rest and During Exercise

	Ejection Fraction (%)		Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)		Double Product* (×10³)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Baseline (n = 22)	39 ± 14	42 ± 18	73 ± 14	116 ± 18	141 ± 14	171 ± 14	10.3 ± 2.3	20.0 ± 2.7
Maintenance† disopyramide (n = 22)	37 ± 9	41 ± 18	75 ± 14	115 ± 18	142 ± 18	176 ± 23	10.6 ± 1.8	20.2 ± 2.5
Disopyramide‡ load (n = 12)	33 ± 10§	35 ± 16§	78 ± 13¶	118 ± 20	140 ± 13	164 ± 13	10.8 ± 2.0	19.4 ± 3.3

* Double product = systolic blood pressure × heart rate/10³. Values expressed are the average of those determined for each patient.
† Disopyramide 150 mg every 6 hours postoperatively for 5 to 10 days (average 7).
‡ Disopyramide given as single 300 mg oral dose.
§ $p < 0.005$ in comparison with ejection fraction determined in these 12 patients before disopyramide.
¶ $p < 0.05$ in comparison with heart rate in these 12 patients before disopyramide.

15% decreased to 33 ± 11% ($p < 0.005$), and the average ejection fraction during exercise decreased from 42 ± 16% to 35 ± 16% ($p < 0.005$). The average systolic blood pressure and double product at rest or with exercise was not significantly changed by the oral disopyramide load, although there was a small increase in the average heart rate at rest (Table I). The correlation between plasma level of disopyramide and change in ejection fraction was not significant at rest ($r = 0.14$) or with exercise ($r = 0.37$). No patient evidenced congestive heart failure after disopyramide. Even 3 of 5 patients with normal resting ejection fraction (>45%) before disopyramide had decreases in ejection fraction after its administration.

Sustained disopyramide therapy: The average ejection fraction at rest (Fig. 2) in the 22 patients during sustained therapy with disopyramide (average serum level 2.5 ± 0.8 μg/ml, range 1.8 to 4.5) of 37 ± 13% was not significantly lower than the average ejection fraction before disopyramide of 39 ± 15%. With exercise, the average ejection fraction of 41 ± 18% on disopyramide also did not differ significantly from that determined at baseline of 41 ± 19%. The average heart rate, systolic blood pressure, and their double product were unchanged at rest or during exercise by disopyramide (Table I).

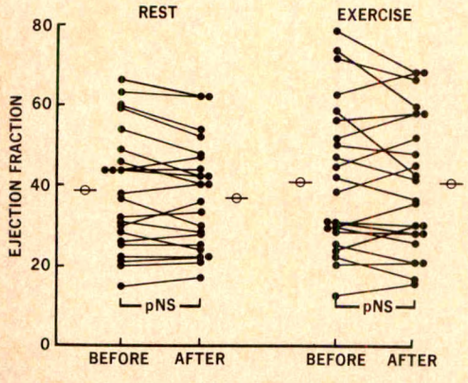

FIGURE 2. Ejection fraction at rest and during maximal supine bicycle exercise in 22 patients before and 5 to 10 days after beginning disopyramide in a maintenance dosage of 600 mg/day in 4 divided doses. The average ejection fraction at rest and during exercise was unchanged during disopyramide, although 3 patients had decreases in ejection fraction during exercise in excess of the test variability. NS = not significant.

Although this dosage of disopyramide was unassociated with a decrease in average ejection fraction for the group as a whole, 3 of 22 (14%) patients had decreases in ejection fraction during exercise in excess of the test variability of 7%. This decrease in ejection fraction during exercise from that obtained before disopyramide ranged from 10 to 16%.

Effects of repeat exercise on ejection fraction: Among the 10 additional control patients in whom rest and exercise studies were repeated without disopyramide 45 to 60 minutes after the first rest-exercise sequence, neither at rest nor with exercise did the second determination of ejection fraction differ significantly from the values obtained during the first sequence (rest 54 ± 4% versus 52 ± 4%, exercise 49 ± 5% versus 47 ± 5%). The interstudy variability for this test sequence was 3 ± 2% at rest and exercise.

Discussion

The results of this study indicate that a single 300 mg oral dose of disopyramide is associated with depression of LV function at rest and during exercise, even in patients with previously normal ejection fraction at rest in whom plasma drug levels did not exceed a therapeutic[1] range. Although depression of ejection fraction was apparent in 6 of 12 patients at rest, in 3 other patients depression of ejection fraction occurred during exercise only. In these 3 patients, the significance of decreases in LV functional reserve in the absence of depression of resting LV function is of uncertain significance. Rather than direct depression of LV systolic function, these changes may reflect myocardial ischemia, consequent to altered loading conditions, or decreased coronary blood flow. Alternatively, they may represent mild depression of the myocardium, unmasked only during exercise stress. Determination of ejection fraction during exercise also increases the sensitivity of radionuclide angiography in detecting LV functional abnormality associated with other noncoronary sources of LV dysfunction.[13–15] Although the single 300 mg dose produced depression of LV function in most patients studied as well as in the average ejec-

tion fraction at rest and during exercise for the group, maintenance dosages of disopyramide were unassociated with a significant decrease in average ejection fraction at rest or exercise. Three (14%) patients did have modest decreases in LV function during exercise only, in excess of study variability, even with this lower dosage. These patients did not have higher plasma drug levels than did the others.

Previous studies, with some exceptions, have indicated an adverse effect of disopyramide on LV function in both experimental animals and man. A decrease in peak-developed tension with disopyramide was documented[5] in guinea pig and rabbit trabecular muscle preparations as well as in human papillary muscle preparations. This decrease was associated with a dose-dependent decrease in superficially located calcium stores. Although depression of myocardial contractility in intact open-chest animals could not be documented by some investigators,[16] Walsh and Horwitz[17] noted myocardial depression and vasoconstriction in conscious, chronically instrumented dogs given disopyramide.

Studies of intravenously administered disopyramide on LV function in man also have been at variance. No adverse hemodynamic effects were noted in patients with normal LV function receiving 1.5 mg/kg of disopyramide intravenously or in individuals with depressed LV function, if heart rate was controlled by atrial pacing.[18] In contrast, Jensen et al[19,20] noted a 28% decline in cardiac index accompanied by an increase in right and LV end-diastolic pressure in patients with overt or subclinical heart failure, and others[21,22] also have described adverse hemodynamic effects after disopyramide 2 mg/kg given intravenously. Although resting LV function was depressed after an intravenous bolus of disopyramide, Thadani et al[23] found that hemodynamic variables during exercise were unaffected, possibly because of enhanced sympathoadrenergic activity. Of note, Kötter et al[24] found that in addition to adverse hemodynamic effects, intravenous disopyramide was also associated with peripheral and coronary arterial vasoconstriction which, in turn, might further compromise myocardial function in susceptible patients.

Although data on the effects of intravenously administered disopyramide have been plentiful, information on the effects of orally administered drug on cardiac performance has been less available. An echocardiographic study[25] documented small decreases in ejection fraction with disopyramide given as a single 200 mg oral dose as well as 4 times daily for 1 week to normal men; however, propranolol produced changes of similar magnitude. Conventional doses of disopyramide in normal subjects also have caused adverse effects on myocardial performance determined by systolic time intervals.[23]

Recently, the onset of clinical manifestations of congestive heart failure was described[9] in 13 of 38 patients receiving long-term oral disopyramide in doses of 300 to 800 mg/day (average serum level 3.4 μg/ml, range 2.2 to 5.6). Objective tests of LV function were not reported in these patients, precluding assessment of the relation between LV ejection fraction and clinical effects. Although no patient had congestive heart failure, our data are consistent with these observations in that most (75%) of our patients receiving a single 300 mg oral dose, in association with an average serum drug level of 3.6 μg/ml, comparable to that just reported, had significant decreases in LV ejection fraction at rest and during exercise. Conceivably, if these higher serum drug levels had been maintained for longer durations, adverse clinical effects may have occurred. Although average ejection fractions at rest or with exercise did not decrease in our patients on "maintenance" disopyramide for 5 to 10 days, and only 4 of these patients had modest decreases in ejection fraction, these patients had substantially lower serum drug levels (average 2.5 μg/ml) than did those just reported on herein. In addition, prolonged exposure to disopyramide may be necessary before cardiotoxic effects are manifested. In our study, LV function was evaluated within a relatively short time (5 to 10 days) after beginning disopyramide therapy. In contrast, some patients described by Podrid et al[9] had the onset of congestive heart failure only after several months of disopyramide therapy. However, 2 of their patients evidenced congestive heart failure within 48 hours of beginning a daily divided disopyramide dose of 600 mg, 8 patients had congestive symptoms during the first 3 weeks, and 1 patient had them 3 hour after a single 300 mg dose. In addition, with the single 300 mg dose, we were able to document a rapid adverse effect on LV function. Hence, both clinical and laboratory manifestations of depressed LV function can be documented within a short time of beginning disopyramide. Concerning the clinical manifestations of congestive heart failure after disopyramide, patients with chronic impairment of LV function are likely to have recurrent pulmonary edema when observed over long intervals, often related to factors other than toxic drug effects. Clinical improvement on drug withdrawal in addition to other therapy for congestive heart failure would not be sufficient to document the drug as the cause of cardiac decompensation. Careful case-controlled studies would be required to identify the contribution of disopyramide or other concurrent medication to such episodes. Also, in patients with poor LV function, large increases in left ventricular filling pressure, and hence pulmonary congestion, may occur in the absence of marked decreases in LV systolic performance. Therefore, although our study shows that ejection fraction may decrease transiently without the onset of pulmonary edema, the absence of a measurable decrease in ejection fraction during sustained disopyramide may not exclude the possibility of a toxic drug effect on cardiac performance.

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Septal Ischemia as a Mechanism of Complete Atrioventricular Block: Demonstration by Thallium Scintigraphy

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Complete atrioventricular block in anterior myocardial infarction usually indicates extensive involvement of the ventricular septum with widespread damage to the conduction system, usually below the undivided bundle of His.[1] The mortality is high.[1–3] Herein we describe a patient with transient complete atrioventricular block caused by transient septal ischemia demonstrated by thallium-201 scintigraphy.

A 65-year-old man with a 5-year history of effort-induced angina pectoris and a 3-year history of repeated syncopal attacks after episodes of chest pain was hospitalized with severe retrosternal pain and recurrent syncope. He was pale and sweating; the pulse was 30 beats/min and blood pressure 170/90 mm Hg. The electrocardiogram showed complete heart block with a slow idioventricular rhythm and a wide QRS complex and right bundle branch block. After a temporary transvenous pacemaker electrode was inserted, he reverted spontaneously to normal sinus rhythm with a normal P-R interval and a pattern of left bundle branch block identical to a tracing taken 6 months previously (Fig. 1). The patient refused to undergo coronary angiography. Another spontaneous ischemic episode associated with sweating occurred the following day, and the atrioventricular block reappeared and was controlled by the pacemaker. A thallium scintiscan (2 mCi of thallium-201) made immediately showed septal ischemia with a 20% decrease in septal perfusion (Fig. 2, left). The remainder of the myocardial uptake of thallium was normal. The pain subsided after 30 minutes and normal atrioventricular conduction returned. A redistribution scan including the area of the septum performed 4 hours later showed normal myocardial uptake (Fig. 2, right). The patient refused further investigation, and a permanent endocardial demand ventricular pacemaker was inserted. He has been well for 6 months, and despite recurrent episodes of chest pain he has not fainted again.

Thallium-201 enters and labels normal nonischemic myocardial cells and is an excellent method of demonstrating regional myocardial perfusion.[4] Ischemia which is induced by stress[5] or develops spontaneously during an episode of pain[6,7] can be demonstrated by scintigraphy; it causes a transient filling defect which disappears during a subsequent redistribution scan.

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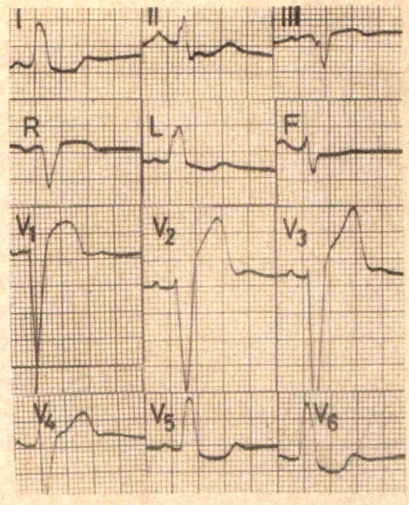

FIGURE 1. Resting electrocardiogram shows a P-R interval of 0.18 seconds, a mean frontal QRS axis of −10°, and complete left bundle branch block.

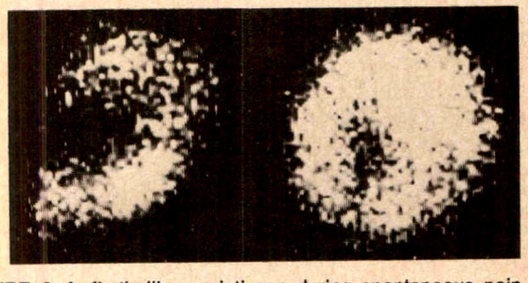

FIGURE 2. Left, thallium scintiscan during spontaneous pain and complete atrioventricular block. Left anterior oblique position. Significant decrease in septal perfusion. **Right,** redistribution scan 4 hours after the episode of complete heart block. Normal septal perfusion.

Left bundle branch block usually masks the diagnosis and the site of myocardial infarction and ischemia. The proximal perforating branches of the left anterior descending artery supply the proximal ventricular septum and the right bundle branch. Septal ischemia, diagnosed with the thallium scintiscan, implied a high lesion of the left anterior descending artery.

This case shows the value of thallium scintigraphy in the intensive care unit to demonstrate the site and nature of transient ischemia of the septum in analyzing the significance and genesis of complete heart block. It established the diagnosis in a patient who refused further investigation and justified the implantation of a ventricular pacemaker.

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Atrial Septostomy as Palliative Therapy for Refractory Primary Pulmonary Hypertension

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Primary pulmonary hypertension (PPH) is an inexorably progressive illness that invariably leads to death. We describe a patient with PPH that was refractory to multiple trials with different vasodilator drugs. A right-to-left shunt using an atrial septostomy catheter was created.

A 22-year-old black woman first presented in 1978 with hemoptysis and dyspnea. Catheterization showed marked pulmonary arterial hypertension with normal cardiac output (Table I). Attempts to lower pulmonary arterial pressure with oral vasodilators including tolazoline, hydralazine, prazosin, captopril, minoxidil, and nifedipine were unsuccessful. Several subsequent catheterizations were performed (Table I). With little else to offer, a right-to-left shunt through an atrial septostomy was created.[1] *A transatrial septal puncture was performed with a Brockenbrough catheter passed through an 8Fr. Mullens sheath. The catheter was then removed and a Park blade septostomy catheter was placed through the sheath into the left atrium. Three successive passages of the catheter were made with the blade open at 30°, 45°, and 90°, respectively. The blade septostomy catheter was then removed and several passages were made with a Rashkind balloon septostomy catheter to further enlarge the newly created atrial septal defect. The effects of the procedure are summarized in Table II. The septostomy caused equalization of pressure between the atria, which resulted in a large right-to-left shunt. Despite the high pulmonary vascular resistance and elevated right-sided pressure, pulmonary blood flow did not decrease after septostomy.*

The patient tolerated the procedure well. The following morning she attempted to get out of bed and sit in a chair but became lightheaded and dyspneic. However, blood gases were unchanged. Later that evening she became more agitated and dyspneic. Repeat blood gases revealed the same partial pressure of oxygen, but the pH was 7.32. Over the next 2 hours, she became more dyspneic and acidotic, developed systemic hypotension, and died.

Necropsy disclosed a 9 mm longitudinal opening in the fossa ovalis and marked right ventricular hypertrophy. In

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TABLE I Results of Serial Catheterizations Since Diagnosis

Date	Systemic Pressure (mm Hg)		Pulmonary Pressure (mm Hg)		Cardiac Output (liters/min)
	Systolic/Diastolic	Mean	Systolic/Diastolic	Mean	
August 1978	115/105	115	120/30	60	5.10
August 1980	130/70	97	117/48	70	3.57
December 1981	150/90	110	150/85	110	2.97
January 1982	100/70	80	175/100	120	2.09

TABLE II Hemodynamic Effects of Atrial Septostomy

	Preseptostomy		Postseptostomy	
	Pressures (mm Hg)	O_2 Saturation (%)	Pressures (mm Hg)	O_2 Saturation (%)
Right atrial mean	22		8	
Pulmonary artery (s/d[m])	175/100 [120]	17	175/100 [125]	15
Left atrial mean	5		8	
Systemic artery (s/d[m])	100/70 [80]	87	125/70 [80]	52
Systemic flow (liters/min)	2.09		5.38	
Pulmonary flow (liters/min)	2.09		2.61	
Right-to-left shunt	. . .		2.77	
Cardiac index (liters/min/m^2)	1.04		2.69	

m = mean; O_2 = oxygen; s/d = peak systolic/end-diastolic.

addition, the left side of her heart was markedly dilated and marked pulmonary venous congestion was present.

Patients with PPH usually develop symptoms from reduced cardiac output,[2] and on initial presentation are often difficult to distinguish from patients with Eisenmenger's physiology from congenital heart disease. However, patients with severe pulmonary hypertension from an atrial septal defect do better than do patients with PPH,[3] possibly because the right side of the heart is able to decompress itself during periods of stress through the right-to-left shunt.[4]

Some patients with PPH have a patent foramen ovale and thus are able to decompress the right side of the heart. Although it has not been clearly demonstrated that these patients do better, a recent retrospective study on patient survival with PPH suggested that this may be the case.[5] We created a right-to-left shunt in our patient because her condition was refractory to medicines and because it was clear that she would die soon. The procedure increased the systemic blood flow without compromising pulmonary blood flow despite the marked right-to-left shunting and the increase in left atrial pressure. That this was beneficial to the patient acutely was confirmed by the fact that she survived initially without other medical support.

The cause of her sudden death is not understood. The findings of acute left ventricular volume overload at necropsy implies that the left ventricle was no longer able to handle a normal preload, as it had 3 years earlier. Although the patient had no clinical signs of left ventricular dysfunction, perhaps left ventricular function is compromised when right ventricular pressure overload develops.[6]

A theoretical basis exists for creating an atrial septal defect in a patient with refractory pulmonary hypertension. Further studies will determine if the creation of an atrial septal defect in patients with PPH will provide long-term benefit.

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Fatal Small Bowel Obstruction After Pacemaker Generator Implantation in the Abdominal Wall

Meir Mazuz, MD
Natesa G. Pandian, MD
Richard E. Kerber, MD

Major complications due to pacemaker implantation are unusual and most often associated with implantation of an epicardial electrode by thoracotomy under general anesthesia. Fatal complications remote from the time of implantation are rare and almost always due to pacemaker malfunction. A case is reported of fatal intestinal obstruction caused by a pacemaker generator which was implanted in the abdominal wall 7 years earlier.

A 69-year-old man was admitted because of abdominal pain, nausea, and vomiting. Nine years earlier a transvenous ventricular demand pacemaker had been implanted because of 2 episodes of syncope associated with left anterior hemiblock on electrocardiogram. Because of pacemaker malfunction, it was replaced 1 year later; because of continued intermittent capture, 1 year later it was replaced again, this time with an epicardial pacing electrode with the generator placed subcutaneously in the left upper quadrant of the abdominal wall. The generator was replaced a fourth time because of abdominal wall pacing thought to be due to a current leak. Thereafter, the patient's condition remained stable for 30 months, when abdominal pain prompted readmission. During his outpatient clinic visits, electrocardiograms and 24-hour Holter monitoring always showed normal sinus rhythm with frequent ventricular premature

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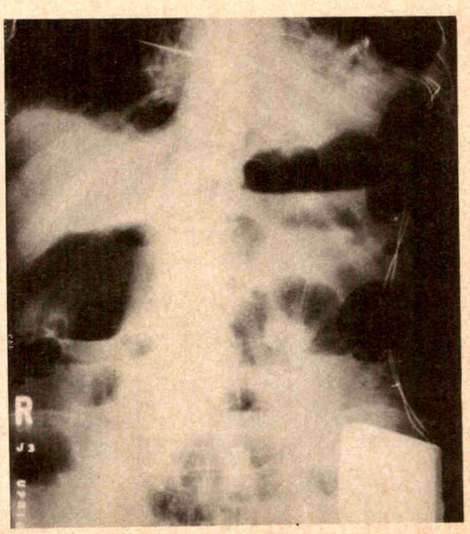

FIGURE 1. Upright abdominal roentgenogram showing multiple dilated loops of small bowel with air-fluid levels. The pacemaker generator implanted in the left lower abdominal wall is visible.

contraction, left anterior hemiblock, and intermittent P-R interval prolongation. Pacemaker rhythm was seen infrequently.

On admission, he had sinus tachycardia (110 beats/min) with occasional ventricular premature contractions. The abdomen was tender, with maximum tenderness over the pacemaker pouch. Bowel sounds were active. The leukocyte count was 13,700 cells/mm^3. The abdominal radiograph (Fig. 1) had a pattern of small bowel obstruction. Initial conservative management of partial intestinal obstruction included nasogastric suction and fluid replacement. After 5 days, laparotomy was performed which revealed a "knuckle" of bowel that was adherent to a suture that had been placed through the peritoneum at the time of generator implantation. This segment of bowel was necrotic and ruptured during surgery. Postoperatively, septic peritonitis, wound dehiscence and evisceration, septic shock, and death occurred (19 days later).

We describe a previously unreported complication from pacemakers: intestinal obstruction related to an intraperitoneal suture placed during generator implantation in the abdominal wall. A related complication has been described.[1] Excessively deep suturing at the time of pacemaker generator implantation should be avoided. Pacemaker-related adhesions may exist in patients who present with evidence of bowel obstruction or other abdominal disease and who have abdominal wall pacemaker generators. A long symptom-free interval since pacemaker implantation does not exclude this possibility.

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Five Coronary Ostia: Duplicate Left Anterior Descending and Right Conus Coronary Arteries

Bruce F. Waller, MD

Multiple aortic coronary ostia are occasionally observed at necropsy. Duplication of an entire major epicardial coronary artery producing an extraaortic ostium, however, has not previously been reported. Recently, I examined the heart of a 57-year-old man who never had symptoms of cardiac dysfunction and died of lymphoma. At necropsy, 5 separate coronary ostia were present (Fig. 1). A right coronary artery and 2 conus arteries arose from the right aortic sinus of Valsalva, and a typical left main artery (with left anterior descending [LAD] and left circumflex divisions) and a duplicate LAD coronary artery arose from the area of the left sinus. Both LAD arteries descended in parallel fashion over the anterior ventricular surface to the cardiac apex.

Five aortic coronary ostia have previously been reported in at least 9 subjects at necropsy,[1,2] but in each the multiple ostia resulted from triplicate conus arteries. Advantages of multiple separate coronary arteries include extra sources of myocardial blood and potential use as collateral arteries. Disadvantages relate to difficulties in recognition and cannulation during coronary angiography or cardiopulmonary bypass procedures.

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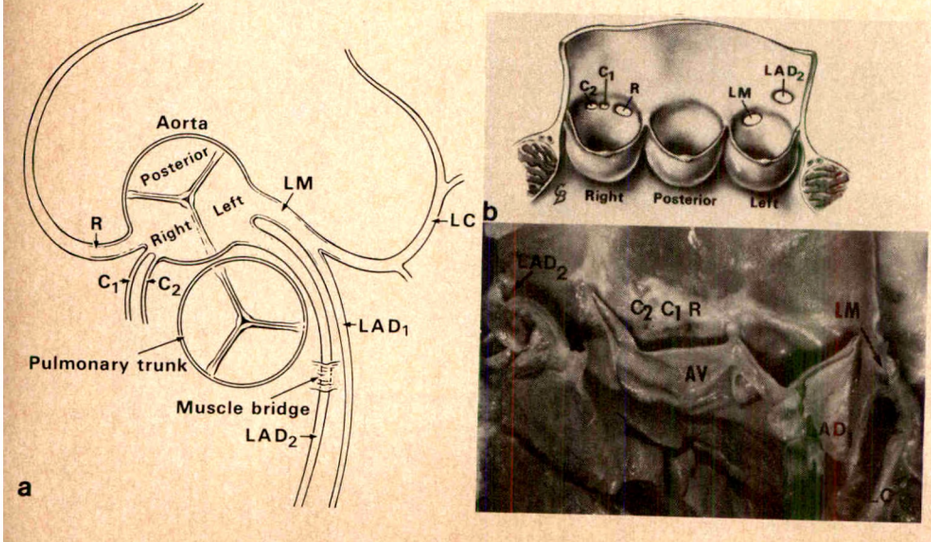

FIGURE 1. Coronary arterial anatomy in a 57-year-old man with 5 coronary ostia (IVAH #81–117). **a,** diagram showing distribution of 6 epicardial coronary arteries resulting from duplicate conus (C_{1+2}) and left anterior descending (LAD_{1+2}) arteries. **b,** drawing of ascending aorta showing location of 5 coronary ostia. The duplicate LAD_2 artery arises slightly above the aortic sinotubular junction. **c,** photograph of opened ascending aorta showing separate origin of 5 coronary arteries. AV = aortic valve; LC = left circumflex; LM = left main; R = right.

Left Atrial Mass: Diagnostic Value of Transesophageal 2-Dimensional Echocardiography and Indium-111 Platelet Scintigraphy

Michael D. Ezekowitz, MD, PhD
Eileen O. Smith, BS
Robert Rankin, MD
Lynn H. Harrison, Jr., MD
Henry F. Krous, MD

Although cardiac myxomas are rare, accurate recognition is essential because excision is usually associated with complete cure. This report demonstrates that although the recognition of this condition by transthoracic, 2-dimensional (2-D) echocardiography is well established,[1] technical difficulties related to obtaining an adequate acoustic window may impair the quality of the image and preclude a definitive diagnosis.[2] These difficulties are minimized by using a transesophageal approach which eliminates the need to transmit the ultrasound through the anterior chest wall and air-filled lungs.[3] This report also demonstrates that myxomas may be mistaken for thrombi by indium-111 platelet scintigraphy, a technique heretofore believed to be specific for thrombosis.[4,5]

A 46-year-old woman with no evidence of preexisting cardiovascular disease presented with a 2-month history of malaise and nonspecific muscle aches. On examination, the only abnormality was an intermittent mid-diastolic rumble heard best at the cardiac apex. Resting electrocardiogram and chest radiograph were within normal limits. Routine M-mode and 2-D echocardiograms were of suboptimal technical quality (Fig. 1). The parasternal long-axis image was suspicious for a left atrial (LA) mass. The apical 4-chamber views were foreshortened, and a definitive demonstration of the mass was not possible. Further investigation was performed by transesophageal 2-D echocardiography and indium-111 platelet scintigraphy.

Before performing the transesophageal 2-D echocardiographic study, the posterior pharynx was anesthetized with a topical benzocaine anesthetic and intravenous diazepam was administered until drowsiness ensued. A modified fiberoptic gastroscope (Fig. 2) was passed through the pharynx into the esophagus and images were obtained (Fig. 3). The method of labelling and imaging platelets has been described previously.[5] Images were obtained in multiple views (Fig. 4).

At surgery, a single LA myxoma 9.0 cm in diameter was successfully removed. The patient recovered uneventfully. By light and electron microscopy, the tumor was characteristic of myxoma. No thrombus was seen on the tumor surface, and scanning electron microscopy failed to disclose platelets adhering to the tumor surface.

From the Departments of Medicine, Surgery, and Pathology, the University of Oklahoma Health Sciences Center. This study was supported by Grant PPG 2 P01 HL 17812-07 from the National Institutes of Health, Bethesda, Maryland, and Veterans Administration Merit Review Grant, Oklahoma City, Oklahoma. Manuscript received December 14, 1982; revised manuscript received January 7, 1983, accepted January 10, 1983.

The interest in this case is twofold. First, we believe that this patient is the first to have LA myxoma demonstrated by transesophageal 2-D echocardiography. Although this form of echocardiographic exami-

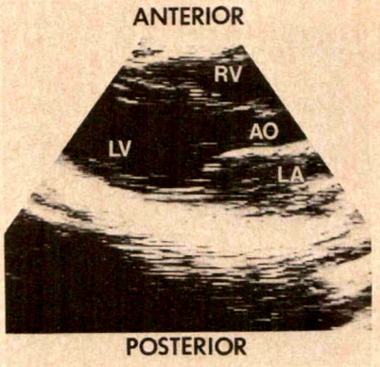

FIGURE 1. A parasternal long-axis 2-dimensional transthoracic echocardiographic image. Within the left atrium is a mass of echoes suggestive of a tumor. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

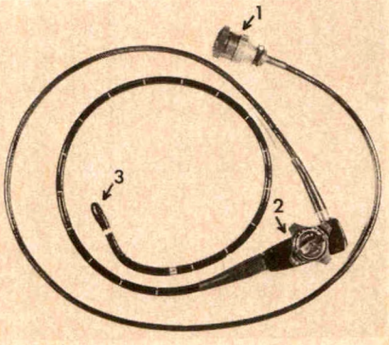

FIGURE 2. A modified Model D Olympus fiberoptic gastroscope. **1** = attachment to Varian 3400 2-dimensional echocardiograph; **2** = mechanism for up and down and lateral movement of gastroscope tip; **3** = gastroscope tip to which is attached a 3.5 mHz transducer. Maximum width of tip is 1.2 cm.

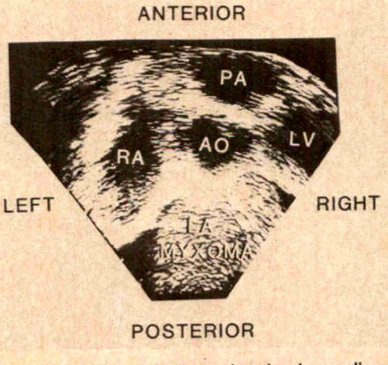

FIGURE 3. Transesophageal 2-dimensional echocardiograph obtained at about the level of the eighth thoracic vertebra. The myxoma is seen within the left atrium. AO = aorta; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium.

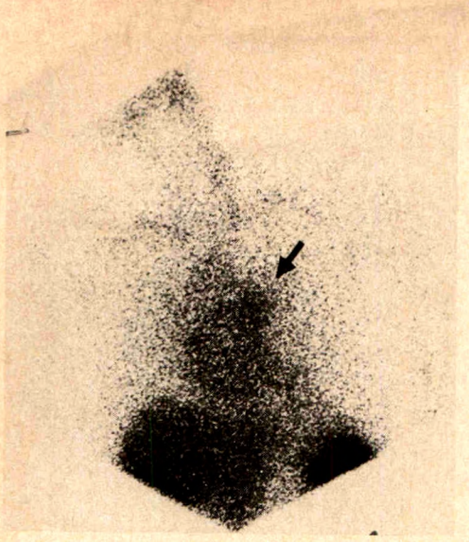

FIGURE 4. Image obtained in the anterior projection 48 hours after injection of the platelet suspension. The top of the image is cephalad. **Arrow** = area of increased activity due to the left atrial myxoma. This activity was maximally positive at 24 to 48 hours after injection of the platelet suspension. The area of increased activity in the right lower zone is caused by the spleen; that seen in the left lower zone is caused by the liver.

nation is associated with more discomfort than the traditional transthoracic approach, the patient was successfully managed without recourse to an invasive procedure. This technique is a viable alternative to cardiac angiography when a definitive diagnosis of LA myxoma cannot be made by regular echocardiographic techniques. Second, this case also is the first demonstration of a nonthrombus presenting as a positive cardiac indium-111 platelet scintiphoto. Platelet scintigraphy is thought to be specific for thrombosis.[4,5] The appearance of myxoma as a positive study demonstrates that cardiac tumors may accumulate platelets on their surface and be mistaken for intracavitary thrombi. An important point of differentiation may be the observation that these images were maximally positive at 24 to 48 hours after injection of the platelet suspension. Thrombi are typically positive at 72 to 96 hours. This difference may suggest transient adherence of platelets to the tumor rather than permanent incorporation as occurs in a thrombus.

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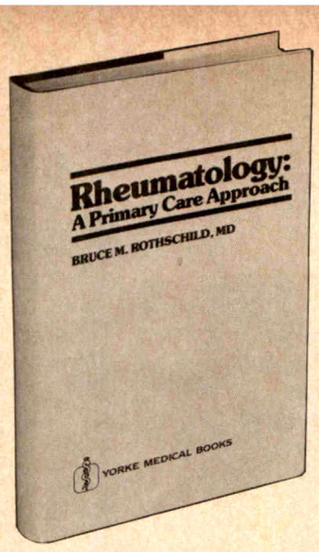

The Diagnosis and Treatment Oriented Approach to Rheumatology with the Primary Care Physician in Mind

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Written by:

Bruce M. Rothschild, MD

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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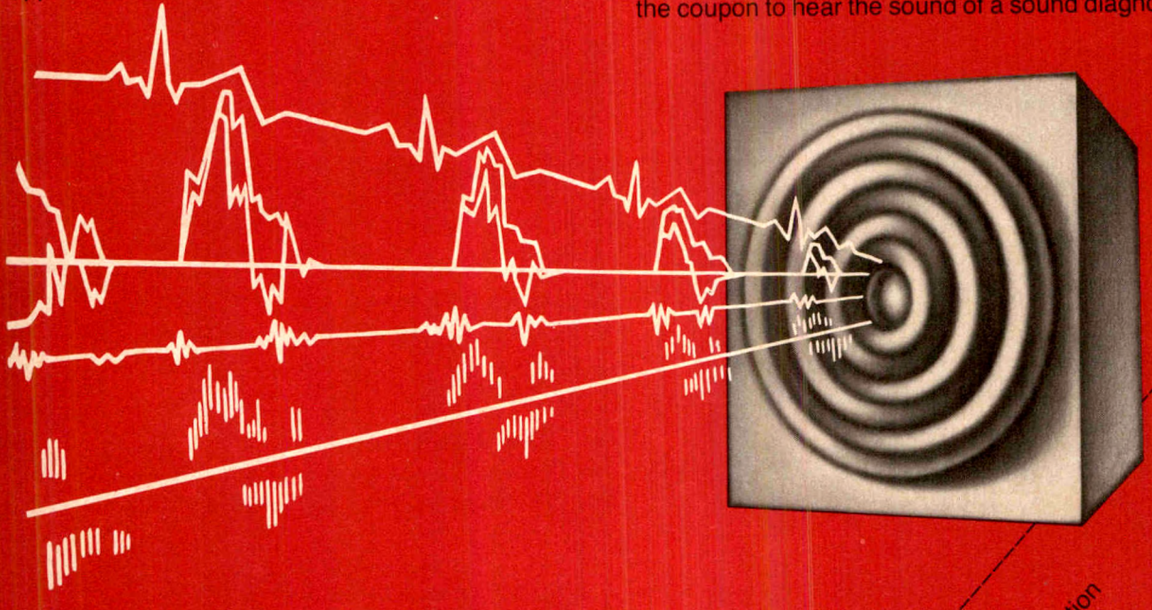

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LETTERS*

DISCRIMINANT FUNCTION ANALYSIS USING THALLIUM-201 SCINTISCANS AND EXERCISE STRESS VARIABLES TO PREDICT CORONARY HEART DISEASE

McCarthy et al[1] constructed discriminant functions from 72 Fourier coefficients of a thallium-201 scan and from treadmill stress test information characterized by 17 variables along with 3 clinical variables. For the population from which they are derived, these functions detect persons with coronary artery disease (CAD) with 92% accuracy and distinguish among persons with no disease, single-vessel disease, and multiple-vessel disease with 78% accuracy. From the information in that report, we believe that these figures are overly optimistic and not reproducible.

The authors developed a discriminant function based on 141 observations and 92 variables which were selected from an even larger group since the use of variables from all 3 views was "not sufficiently more accurate in predicting the presence of CAD than using the Fourier coefficients from the 30 degree left anterior oblique view alone." Their use of a partial F of 8 for variable selection shows that they are aware of the difficulties with multiple comparisons, especially with a limited number of observations. Use of this conservative F value will help prevent spurious factors from being declared significant. The sheer number of candidate variables examined would still be expected to cause problems of reliability and stability of the model.

Although the jackknife procedure eliminates bias in the estimation-classification process based on a single, prechosen statistical model, it does not eliminate the bias caused by variable selection. The estimate of accuracy may be higher than what one would observe when the final model is used to predict CAD in an entirely new patient sample.

A technique preferable to allowing so many variables to be candidates is to develop summary indexes based on clinical intuition and to let such summary indexes be used in a modeling procedure such as the authors have used. As Marquardt and Snee[2] have noted, "It is better to use a little bit of all the variables than all of some variables and none of the remaining ones." Better predictive models which are more interpretable can be obtained by imposing more structure on the problem (even by using subjective evaluations of the scintiscans) than by requiring each of the Fourier coefficients or treadmill measurements to be considered independently.

Finally, it is difficult to know the clinical importance of the discriminant functions because the clinical characterization of the patients is incomplete. Knowing only the sex of the patient, one can correctly classify presence of disease 84% of the time in this population, compared with a 92% accuracy based on the much more complicated data. Other clinically important factors such as type of angina and patient risk factors would improve on this 84%. Thus, when describing the benefits of new technology, it is important to compare the new procedures with results that can be obtained using routinely available information. The true incremental yield of a new test can then be qualified and properly evaluated.[3]

Ray McKinnis, PhD
Frank E. Harrell, Jr., PhD
Kerry Lee, PhD
Durham, North Carolina

1. **McCarthy DM, Sciacca RR, Blood DK, Cannon PJ.** Discriminant function analysis using thallium-201 scintiscans and exercise stress test variables to predict the presence and extent of coronary artery disease. Am J Cardiol 1982;49(June):1917–1926.
2. **Marquardt DW, Snee RD.** Ridge regression in practice. Am Stat 1975;29:4.
3. **Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA.** Evaluating the yield of medical tests. JAMA 1982;247:2543–2546.

REPLY: McKinnis, Harrell, and Lee express concern that the statistical model employed in our recent study may have yielded unrealistic results regarding the ability to classify patients suspected of having CAD. We agree that stepwise procedures are susceptible to problems.[1]

One problem is that when considering a large number of candidate variables, there is an increased chance of falsely declaring a variable to be a significant addition to the model. The Bonferroni-type approach[2] of using a cutoff partial F value of 8 was an attempt to deal with this problem; the smallest partial F value actually observed (13.05) corresponds to a p value of 0.05 for 92 independent variables considered jointly. Thus, we are fairly confident that the variables selected have some predictive power.

A second consideration regarding reliability arises when variables which comprise the model are not statistically independent. Attempts to circumvent this problem have led to consideration of biased estimators with smaller variances than the classic least-square estimates.[3] For the model in our study, the square of the largest multiple correlation coefficient between any one of the predictor variables and the rest of the predictor variables was only 0.3, indicating that the predictor variables are not highly intercorrelated.

The suggestion that summary indexes based on clinical intuition be developed for modeling purposes is interesting but difficult to apply. As noted in our report, candidate variables from the electrocardiographic stress test were selected on the basis of previous reports of their utility in predicting the presence or extent of CAD. For the Fourier amplitude coefficients, no previous experience was available other than the theoretical consideration that low-frequency components of the transform contain more useful information than high-frequency components. Visual scan interpretations were specifically excluded from consideration because we were seeking to develop an *objective* method as an alternative to subjective evaluation, which has significant interobserver disagreement.[4]

To determine the accuracy of the discriminant function, we employed the jackknife procedure.[5] While a stepwise analysis will introduce an additional degree of bias to the jackknife procedure, the amount of this additional bias may not be large. Also, as noted, it is important to consider prior information in evaluating the utility of any classification rule. The observation that coronary artery disease could have been predicted with 84% accuracy on the basis of classifying all males as having CAD and all females as normal is true but misleading. The more relevant observation is that the discriminant function was significantly predictive of CAD for both the male and female subpopulations with vastly different prevalence of CAD (the predictive accuracy was 93% for males and 88% for females).

Although statistical methods can be helpful in determining the validity of a model of this type, the best evaluation is by application to a different group of patients. To this end, we are currently testing the discriminant functions in a prospective study of an additional 100 patients undergoing thallium scintigraphy and coronary arteriography. Preliminary results show that the discriminant function employing just Fourier amplitude coefficients, which had an estimated accuracy of 89% in our original report, results in an accuracy of 85%. Employing prior estimates of the probability of CAD based upon age, sex, and anginal pattern,[6] the predictive accuracy is 88%. Although this increase in overall predictive accuracy is small, 48% of the CAD patients are predicted to have disease with a probability exceeding 99%. Thus, while incorporation of prior information can be demonstrated to enhance the certainty of the predictions, these preliminary results suggest that the model is reliable for detecting CAD.

David M. McCarthy, MD
Robert R. Sciacca, EngScD
David K. Blood, MD
Paul J. Cannon, MD
Philadelphia, Pennsylvania

1. **Mosteller J, Tukey JW.** Data Analysis and Regression: A Second Course in Statistics. Reading, MA: Addison-Wesley, 1977.
2. **Neter J, Wasserman W.** Applied Linear Statistical Models. Homewood, IL: Richard D. Irwin, 1974.
3. **Marquardt DW, Snee RD.** Ridge regression in practice. Am Stat 1975;29:2–30.
4. **Trobaugh GB, Wackers FJTh, Sokole EB, DeRouen TA, Ritchie JL, Hamilton GW.** Thallium-201 myocardial imaging: an interinstitutional study of observer variability. J Nucl Med 1978;19:359–363.
5. **Lachenbruch PA.** An almost unbiased method of obtaining confidence intervals for the probability of misclassification in discriminant analysis. Biometrics 1967;23:639–645.
6. **Diamond GA, Forrester JS.** Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–1358.

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

GLUCOSE-INSULIN-POTASSIUM INFUSION IN ACUTE MYOCARDIAL INFARCTION

Whitlow et al[1] presented data for 28 (66%) of 42 patients, originally randomized with a diagnosis of suspected myocardial infarction (MI), to either a control group or a group treated with a glucose-insulin-potassium (GIK) infusion. Ten randomized patients were excluded from the analysis because they did not have a diagnostic increase in plasma CK-MB, and in some of these treatment may have prevented MI. Four other randomized patients were excluded because radionuclide scans were not performed.

We would be interested in seeing analysis of the hemodynamic, cardiac catheterization, radionuclide data, and mortality on *all* randomized patients, where these data are available. This would show the effect of GIK treatment on an "intention-to-treat" basis and would remove any biases introduced by excluding patients from the final analysis. In addition, it would be possible to see whether GIK infusion can reduce the probability of MI developing in patients with threatened MI, as has been shown by early intervention studies of intravenous beta-blockers.[2]

Rory Collins, MD
Salim Yusuf, MD
Oxford, England

1. **Whitlow PL, Rogers WJ, Smith LR, McDaniel HG, Papapietro SE, Mantle JA, Logic JR, Russell RD, Rackley CE.** Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. Am J Cardiol 1982;49(Mar):811–820.
2. **Yusuf S, Peto R, Bennett D, Ramsdale D, Furse L, Bray C, Sleight P.** Early intravenous atenolol treatment in suspected acute myocardial infarction. Lancet 1980; 2:273–276.

REPLY: We certainly appreciate the inquiry of Collins and Yusuf. Much of the data they request appears in abstract form[1] for the entire group of patients studied in our institution. To summarize, 190 patients admitted within 12 hours of chest pain were randomized to glucose-insulin-potassium (GIK) infusion (95 patients) or control infusion (95 patients). Acute myocardial infarction was confirmed enzymatically in 64% (61 of 95) of GIK patients versus 77% (73 of 95) of controls ($p < 0.06$). The group of patients without confirmed myocardial infarction were urged to undergo cardiac catheterization within 1 week after randomization. Many of these patients were treated surgically, and therefore the 2-week postrandomization data are not comparable to the group of patients treated medically. In the subgroup of patients originally randomized the referred to by Collins and Yusuf, hospital mortality was 0% in both groups. The hemodynamic, cardiac catheterization, radionuclide, and mortality data on all randomized patients is the subject of a planned report.

Patrick L. Whitlow, MD
William J. Rogers, MD
Birmingham, Alabama

1. **Rogers WJ, McDaniel HG, Mantle JA, Rackley CE.** Glucose-insulin-potassium infusion in acute myocardial infarction—results of a prospective randomized study. Clin Res 1982;30:216A.

FOLLOW-UP OF PATIENTS HAVING EITHER TRANSVENOUS CATHETER ABLATION OF THE ATRIOVENTRICULAR JUNCTION OR DIRECT SURGICAL HIS BUNDLE DISRUPTION

A new technique for transvenous catheter ablation of the atrioventricular junction was recently described.[1,2] At a recent meeting of investigators using this technique, it was estimated that approximately 70 patients throughout the world underwent this procedure. To assess the efficacy and safety of this procedure, we need follow-up data for these patients. We have, therefore, instituted a registry to allow accumulation and analyses of these data. In addition, to compare the newer technique with standard cardiac-surgical techniques for His bundle ablation, we plan to accumulate similar data for these patients who have undergone direct surgical attempts at His bundle disruption. If you, or colleagues at your institution, have been involved in any of these procedures, please contact *Melvin Scheinman, MD, Room 573, Moffitt Hospital, University of California, San Francisco, California 94143*, telephone (415) 666-1035.

The appropriate forms will be sent to you directly to allow entrance of your data in the registry. Individual patient and institution confidentiality of this data will be strictly enforced. We plan to furnish you with biannual follow-up data from the registry.

Ad Hoc Committee on Transvenous A-V Junctional Ablation

1. **Scheinman MM, Morady F, Hess DS, Gonzalez R.** Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. JAMA 1982;248:851–855.
2. **Gallagher JJ, Svenson RH, Kasell JH, et al.** Catheter technique for closed-chest ablation of the atrioventricular conduction system: a therapeutic alternative for the treatment of refractory supraventricular tachycardia. N Engl J Med 1982;306:194–200.

CATHETER DEFIBRILLATION

The current surge of interest in catheter defibrillation makes it particularly important that those who are now entering the field be thoroughly acquainted with the historical background of the technique. I am referring especially to a report by Yee et al,[1] suggesting that the authors may not be aware of the early work. In contrast to the information provided, the concept of a single intravascular catheter defibrillating system originated with Mirowski et al,[2] who also implemented and applied it to the clinical setting.[3,4]

Morton M. Mower, MD
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1. **Yee R, Zipes DP, Gulamhusein S, Kallok MJ, Klein GJ.** Low energy countershock using an intravascular catheter in an acute cardiac care setting. Am J Cardiol 1982;50 (Nov):1124–1129.
2. **Mirowski M, Mower M, Staewen WS, Denniston RH, Tabatznik B, Mendeloff AI.** Ventricular defibrillation through a single intravascular catheter electrode system (abstr). Clin Res 1971;19:328.
3. **Mirowski M, Mower MM, Staewen WS, Denniston RH, Mendeloff AI.** The development of the transvenous automatic defibrillator. Arch Intern Med 1972;129:773–779.
4. **Mirowski M, Mower MM, Gott VL, Brawley RK.** Feasibility and effectiveness of low-energy catheter defibrillation in man. Circulation 1973;47:79–85.

COMPARISON OF VERAPAMIL AND NIFEDIPINE IN CHRONIC STABLE ANGINA PECTORIS

We wish to draw your readers' attention to certain aspects of a recent report in your Journal by Bala Subramanian et al.[1] As far as we are aware, it is neither normal nor recommended clinical practice to commence the prescription of nifedipine at 20 mg 3 times a day, particularly when many patients have not had any previous antianginal therapy. Such doses might be applicable if control was inadequate with a beta-blocking drug, but Fox et al[2] previously suggested careful titration of nifedipine dosage since individual responses vary.

It is stated that 32 patients commenced the study and 3 were withdrawn from the nifedipine group before the fortnightly review. It is then stated that a further 4 patients were withdrawn at this review because of dose-related chest pain associated with tachycardia and S-T depression. The fate of the fourth patient who was withdrawn is not apparent, and the penultimate paragraph of the report states that 7 patients had aggravation of angina while taking nifedipine. It is not at all clear whether the analysis involves 25 patients receiving nifedipine, but certainly 28 could not have completed the study as stated.

The experience of these investigators is very different from the report of Dawson et al[3] from Hillingdon Hospital, who wisely introduced nifedipine in a 10 mg 3 times a day dosage for the first 3 days before increasing to 20 mg 3 times a day. In that study, the 2 drugs employed in identical dosage to the Northwick Park regime were equipotent in terms of efficacy, though side effects were less frequent on verapamil. With a more cautious approach no patient developed aggravation of angina from nifedipine. Moreover, the lack of effect of nifedipine on S-T depression during Holter monitoring is in sharp contrast to the effects described by Lynch et al.[4]

The investigators are aware of our concern about the placebo they used, for it is hard to accept that orange capsules bought commercially and filled with water are indistinguishable from the characteristic peppermint taste and smell of nifedipine and matching placebo available from Bayer.

H. B. Allen, MA, MB, BCh
G. Macdonald, MB, ChB
Haywards Heath, West Sussex, England

1. **Bala Subramanian V, Bowles MJ, Khurmi NS, Davies AB, Raftery EB.** Randomized double-blind comparison of verapamil and nifedipine in chronic stable angina. Am J Cardiol 1982;50(Oct):696–703.
2. **Fox KM, Deanfield J, Jonathan A, Selwyn A.** The dose-response effects of nifedipine of ST segment changes in exercise testing: preliminary studies. Cardiology 1981;68:Suppl 2:209–212.
3. **Dawson JR, Whitaker NHG, Sutton GC.** Calcium antagonist drugs in chronic stable angina: comparison of verapamil and nifedipine. Br Heart J 1981;46:508–512.
4. **Lynch P, Dargie H, Krikler S, Krikler D.** Objective assessment of antianginal treatment: a double-blind comparison of propranolol, nifedipine and their combination. Br Med J 1980;1:184–187.

REPLY: Thirty-two patients initially were included in the trial; 4 were withdrawn before completing any evaluation on any active

drug. One was withdrawn in the placebo phase due to hypochromic anemia, and 3 developed side effects to nifedipine. Four more developed side effects to nifedipine therapy and did not want to continue beyond 2 weeks; all objective assessments had been completed at 2 weeks and therefore data were included for analysis.

It is difficult to compare the results of the current study with those of the Dawson or the Lynch study. The study of Dawson et al included 16 patients who were chosen because they did not respond to beta-adrenergic blocking drugs and nitrates. They used Bruce's protocol in contrast to our modified Balke's protocol and did not specify the actual treadmill exercise time required to produce angina but used calculated maximal VO_2. Their data show clear differences between verapamil and nifedipine which did not reach statistical significance, perhaps due to the small number of patients. The number of anginal attacks was reduced from 11 on placebo to 3 on verapamil ($p < 0.01$) and 6 on nifedipine ($p < 0.05$). Similarly, the glyceryl trinitrate consumption was reduced from 9 on placebo to 3 on verapamil and 5 on nifedipine. The predicted VO_2 max was 23 ± 1.5 ml/kg/min on placebo and increased to 26 ± 1.4 ml/kg/min on verapamil ($p < 0.001$). Nifedipine increased the value to 25 ± 1.5 ml/kg/min ($p = 0.05$). The improvement in exercise time noted in our trial on nifedipine was 39%, which is similar to the results published by the American multicenter double-blind trial on nifedipine.[1] That report showed a 38% improvement on a mean dose of 51 mg/day, in contrast to the Dawson study, which showed an increase in VO_2 max of 11%. Even the decision of Dawson et al to increase the dose of nifedipine gradually did not prevent a frequency of palpitations of 38% (6 of 16) compared with 25% in our group. The English data sheet on nifedipine (Adalat) does not specify the need for dose titration and informs that the recommended dose is 10 mg 3 times daily but that, if necessary, up to 2 capsules 3 times daily may be taken.[2]

In their study Lynch et al used an Oxford medilog direct recording AM tape system which is unreliable for measuring S-T segment changes.[3,4] Bragg-Remschel et al[4] state that "with the exception of the Oxford AM system which introduces so much additional S-T depression that using it for S-T segment studies would seem unwise, probably all of the manufacturers evaluated could be considered acceptable for grossly reproducing S-T segment depression." Lynch et al used visual methods of S-T segment analysis which are neither accurate nor free from observer variations. It is unreasonable to compare such a study with the current one, which used frequency modulated tape recording and precise computerized digital analysis of S-T segments and heart rate.

The placebo capsules were identical in appearance to the active drug. It is unreasonable to expect that a placebo should taste and smell identical to the active drug. Further, the contention has no relevance because the patients were specifically asked to swallow all drugs with water and never chewed them, a procedure which kept the characteristic nifedipine taste within the capsules. It makes one wonder whether Bayer UK may demand the use of a placebo that produces the characteristic facial flush as nifedipine does, which can be claimed to be a factor influencing all double-blind trials using nifedipine.

V. Bala Subramanian, MD
Harrow, Middlesex, England

1. **Mueller HS, Chahine RA.** Interim report of multicenter double-blind, placebo controlled studies of nifedipine in chronic stable angina. Am J Med 1981;71:645–657.
2. **Association of British Pharmaceutical Industries.** Data sheet compendium 1983–84: Adalat. London: Datapharm Publications, 1983:116.
3. **Bala Subramanian V, Lahiri A, Green HL, Stott FD, Raftery EB.** Ambulatory ST segment monitoring. Problems, pitfalls, solutions and clinical application. Br Heart J 1980;44:419–425.
4. **Bragg-Remschel DA, Anderson CM, Winkle RA.** Frequency response characteristics of ambulatory ECG monitoring systems and their implications for ST segment analysis. Am Heart J 1982;103:20–31.

ATRIOVENTRICULAR NODAL REENTRY

Scheinman et al[1] reported a case of atrioventricular nodal reentry in which they purport to show that the atrium is not an integral part of the tachycardia reentry circuit. This conclusion is based on the following observations. First, burst pacing of the high right atrium at a cycle length shorter than that of the tachycardia captured the right atrium and atrium in the region of the His bundle catheter without altering the tachycardia cycle length (Figure 2 of their report). Examination of their figure, however, indicates that the tachycardia cycle length was not constant. We have taken their figure, enlarged it, and added a ladder diagram (our Fig. 1). Our caliper measurements indicate that the R-R intervals during the tachycardia progressively shorten by up to 25 ms. Our measurements are calculated from the time scale provided by the authors. We note, however, that in the figure in question, the intervals between the heavy vertical lines (presumably time interval markers) are not constant and vary by 25 ms, suggesting that the paper recorder speed may not have been constant. If this were so it would obviously invalidate the findings of the authors.

We believe an alternative explanation is possible. Atrial pacing could have resulted in capture of the ventricles by the slow atrioventricular nodal pathway with a Wenckebach sequence (see ladder diagram). Since during atrioventricular nodal reentry tachycardia the atrioventricular node is operating close to its functional refractory period, invasion of the tachycardia circuit could be expected to produce only slight advancement of each QRS complex. It should be noted that to obtain our measurements we had to assume a constant paper recording speed.

The second observation, that a premature atrial depolarization in the high right atrium advanced the septal atrial electrogram without affecting the tachycardia (Figure 3 of their report), also bears critical examination. According to our measurements, the fourth QRS complex in Figure 3 is 5 to 10 ms earlier than expected, indicating that the slow pathway of the tachycardia circuit may have been invaded by the premature atrial stimulus leading to premature His bundle and ventricular depolarization.

Essential to the correct interpretation of any electrophysiologic study is the accurate measurement of data. From the published information we cannot agree with the authors' conclusions that in this patient the atrium was not part of the reentry circuit. The perplexing question of whether the atrium is a necessary part of the reentry circuit in atrioventricular reentrant tachycardia remains, in our view, unanswered.

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Richard W. Harper, FRACP
Melbourne, Australia

1. **Scheinman MM, Gonzales R, Thomas A, Ullyot D, Bharati S, Lev M.** Re-entry confined to the atrioventricular node: electrophysiologic and anatomic findings. Am J Cardiol 1982;49(May):1814–1818.

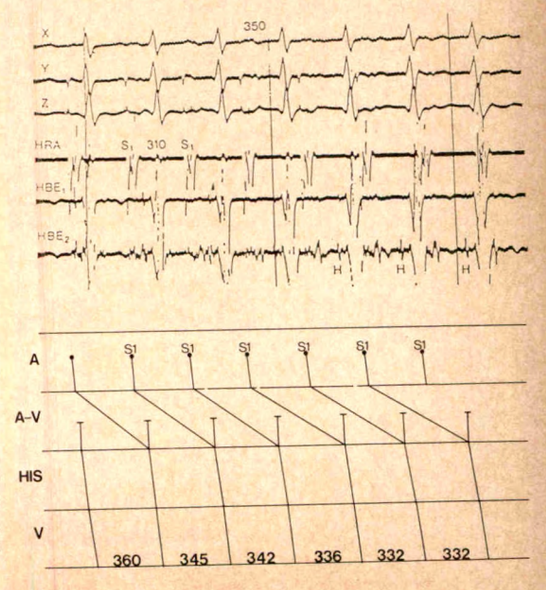

FIGURE 1. Ladder diagram illustrating our explanation for Figure 2 in the report of Scheinman et al.[1] A = atrium; A-V = A-V node; His = His bundle; V - ventricle. Measurements of the intervals between each QRS complex are in milliseconds.

REPLY: Your measurements are accurate, and on review of the study we found that during rapid atrial pacing, clear-cut shortening of the cycle length uniformly occurred just before tachycardia termination. I therefore agree that a Wenckebach sequence is likely. However, during initiation of atrial pacing, 1 or more atrial complexes were clearly dissociated from the tachycardia. Dissociation of the recorded atrial electrograms has been previously described in patients with atrioventricular nodal reentrant tachycardia. However, neither these studies nor our own observations during electrophysiologic studies conclusively exclude the possibility of a small atrial link in the tachycardia circuit. The careful histologic studies by Lev and Bharati are important in that a distinct atrionodal or atrial-His pathway was not found. These observations support the thesis that the atrium is not a necessary link in the tachycardia circuit.

Melvin Scheinman, MD
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VENTRICULAR FUNCTION BEFORE AND AFTER REPAIR OF TETRALOGY OF FALLOT

In their report on ventricular function in pre- and postoperative tetralogy of Fallot, Lange et al[1] separate their patient groups on the basis of a total right ventricular volume load. This volume is calculated on the basis of combined pulmonic regurgitant volume plus left-to-right ventricular septal defect (VSD) flow, and the separate contributions of each are not reported. They justify this on the basis that the end-diastolic volume (EDV) bears a similar relation to the quantity of additional flow through the right ventricle, whether that flow is derived from pulmonic regurgitation or VSD. However, these patients also are considered to have right ventricular dysfunction, which means that a normal ventricular function curve cannot be assumed, and hence EDV is not determined solely by the degree of volume loading.[2] Although some diastolic VSD flow can at times be noted, there is predominantly a systolic right ventricular volume load in contrast to the purely diastolic volume load of pulmonic regurgitation. The significance of an elevated EDV is therefore quite different in the 2 situations and would hardly justify pooling the data.

By combining these patients, the authors also render it difficult to interpret the right ventricular ejection fraction (EF) results. The systolic loading through a residual VSD will augment right ventricular ejection impedance. Because EF is inversely related to afterload, EF would be expected to decrease.[3] The volume load of pulmonic regurgitation results in enhanced preload without afterload augmentation, producing an increase in EF.[3] Clearly, a reduced EF in this situation has far different significance than a reduced EF with residual VSD. Separate reporting of these data would have facilitated these interpretations.

Finally, the authors interpret a reduced left ventricular EF in the preoperative patient with tetralogy of Fallot as indicative of impaired myocardial function. In the patient with unrepaired tetralogy of Fallot, the flow from right to left through the VSD results in reduced pulmonary blood flow. This results in a decrease in left ventricular preload, which would result in a reduced EF.[4] In contrast to the statement by Lange et al,[1] the VSD in the patient with unrepaired tetralogy of Fallot would *not* reduce ejection impedance. With the right-to-left systolic shunt, a net increase in ventricular afterload would be predicted, thereby reducing EF. In the presence of preload and afterload changes that could reduce EF, it is unwarranted to conclude that the observed reduction in EF is due to an abnormal contractile state. The primary issue to be settled here is whether there is any underlying abnormality of contractile function in tetralogy of Fallot and whether deterioration of myocardial function occurs with time. EF is a nonspecific index and cannot settle this issue. Other techniques are necessary to differentiate myocardial dysfunction from altered loading conditions.[5]

Steven Colan, MD
Boston, Massachusetts

1. **Lange FL, Onnasch DGW, Bernhard A, Heintzen PH.** Left and right ventricular adaptation to right ventricular overload before and after surgical repair of tetralogy of Fallot. Am J Cardiol 1982;50(Oct):786–794.
2. **Ross J Jr.** Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976;18:255–264.
3. **Mahler F, Ross J Jr, O'Rourke RA, Covell JW.** Effects of changes in preload, afterload, and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 1975;35:626–634.
4. **Parker JO, Case RB.** Normal left ventricular function. Circulation 1979;60:4–12.
5. **Borow KM, Neumann A, Wynne J.** Sensitivity of end-systolic pressure-dimension and pressure volume relations to the inotropic state in humans. Circulation 1982;65:988–997.

REPLY: Colan's comments should further stimulate the discussion on the applicability of experimentally derived concepts to clinical medicine. He doubts that in patients with tetralogy of Fallot postsurgical repair chronic volume overloading of the right ventricle during systole secondary to a residual ventricular septal defect (VSD) and during diastole secondary to pulmonic regurgitation may have similar effects on size and function of the right ventricle. We certainly evaluated carefully our data with respect to this question and thought we discussed this point sufficiently in our report. Colan is right, that end-diastolic volume (EDV) is not solely determined by the degree of volume load. Preload is important, especially when acutely altered as has been shown in animal studies of the left ventricle.[1] In our patients with chronic volume loading of the right ventricle after surgical repair of tetralogy of Fallot, we assumed a comparable stable basal state during the cardiac catheterization procedure under light sedation. In this state the observed depressed ejection fraction (EF) indicates a maximally utilized preload reserve according to the concept of Ross.[1] Thus, we assume that EDV is mainly determined by the degree of chronic volume loading, justifying pooling of the data.

Colan's statement that chronic systolic loading through a residual VSD augments ejection impedance of the right ventricle, thereby reducing EF, is unproven. In pure systolic loading in children with a classic singular VSD without pulmonary hypertension, EF is normal in the presence of an elevated EDV.[2,3] This indicates that dilatation of the right ventricle can be due to chronic systolic volume overloading. If ejection impedance is chronically increased, as in valvular pulmonic stenosis, one would expect in children a normal EDV and an EF at the upper limit of normal.[3]

Colan's statement that reduced pulmonary flow in unrepaired tetralogy of Fallot results in a decrease in left ventricle preload, which would result in a reduced EF, is speculative. As proof he cites the work of Parker and Case.[4] These authors developed a concept of normal left ventricle function in man we fully agree with.[5] They state that for the normal left ventricle, significant preload dependency exists only for end-diastolic filling pressures <10 mm Hg. In experimental dogs, acute decrease of preload resulted indeed in a reduction of ejection phase indexes.[1] In our patients with unrepaired tetralogy of Fallot, however, end-diastolic pressures were normal and it can be expected that the left ventricle has adapted its size to the chronically reduced preload secondary to the reduced pulmonary flow. In fact, pulmonary flow has always been diminished, even during the developmental phase.

We cannot agree with the statement of Colan that the right-to-left shunt would increase afterload of the left ventricle, thereby reducing EF. During the period of ejection into the aorta, pressure in the aorta and thus afterload is normal. During the preejection phase with respect to aortic ejection there is a left-to-right shunt through the VSD, which probably causes a reduction of impedance compared with a normal hemodynamic situation.[6] In contrast to Colan, we would not expect to find an increased impedance. In children with chronic pressure overload, as in valvular aortic stenosis, EF tends to be elevated,[7] which is contrary to the reduction of EF found after acute increase of afterload in experimental animals. Therefore, we maintain that the reduced left ventricular EF in unrepaired tetralogy of Fallot suggests impaired global myocardial function.

We agree with Colan that a pressure stress in patients after repair of tetralogy of Fallot would be helpful in assessing myocardial function of the left ventricle, especially if EF is normal. Adopting the concept of Ross,[1] our patients with a reduced EF during the cardiac catheterization procedure under light sedation would be in a "depressed basal state." The preload reserve is expected to be practically utilized. Any further afterload increase of even moderate degree would result in a further reduction of EF. Accordingly, myocardial function of the left ventricle after surgical repair of tetralogy of Fallot did remain depressed.

In general, it is difficult to apply concepts based mainly on acute loading experiments

of the left ventricle in open-chest animals or isolated heart preparations to the chronically overloaded right ventricle of children with surgically repaired congenital heart diseases.

Peter E. Lange, MD
Dietrich D. W. Onnasch, PhD
Alexander Bernhard, MD
Paul H. Heintzen, MD
Kiel, West Germany

1. **Ross J.** Afterload mismatch and preload reserve. A conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976;18:255–264.
2. **Graham TP, Atwood GF, Boucek RJ, Cordell D, Boerth RC.** Right ventricular volume characteristics in ventricular septal defect. Circulation 1976;54:800–804.
3. **Lange PE, Onnasch D, Beurich HW, Heintzen PH.** Angiocardiographic right ventricular volume determination. In: Kaltenbach M, Lichtlen P, eds. Coronary Heart Disease III. Stuttgart: Thieme Verlag, 1978:219–227.
4. **Parker JO, Case RB.** Normal left ventricular function. Circulation 1979;60:4–12.
5. **Lange PE, Onnasch DGW, Schaupp GH, Zill C, Heintzen PH.** Normal size and function of the human left and right ventricles during growth. Pediatr Cardiol, in press.
6. **Lange PE, Onnasch DGW, Heintzen PH.** Größe, Form, Funktion und Lage des linken Ventrikels bei Kindern mit Aortenstenose. Z Kardiol 1982;71:236.
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DEGENERATION OF ANTIDROMIC TACHYCARDIA INTO ATRIAL FIBRILLATION IN THE WOLFF-PARKINSON-WHITE SYNDROME

Cosio et al[1] recently highlighted the possibility of transition of an antidromic reciprocating tachycardia to atrial fibrillation (AF) with a rapid ventricular response. We also observed similar features in a patient.

A 41-year-old woman had in the last 5 years frequent attacks of AF with a fast ventricular response and large QRS complexes. During attacks she was hypotensive and prostrated. With sinus rhythm, signs of intermittent Wolff-Parkinson-White syndrome type A were found, which were rate-dependent and present only at heart rates >100 beats/min. At the onset of electrophysiologic study, the A-H interval was 95 ms and the H-V interval 35 ms (Fig. 1A). During the study, orthodromic and antidromic tachycardias were easily provoked by programmed atrial pacing (Fig. 1, B and C). Orthodromic tachycardia exhibited a curious alternation from a normal conduction pattern to incomplete right bundle branch block with associated alternation of cycle length duration (Fig. 1B). Antidromic tachycardia spontaneously degenerated into AF with a minimal R-R interval of 185 ms (Fig. 1D). After application of Ethmozin, a short-lasting transition of AF to atrial flutter was seen (Fig. 1E). Atrioventricular conduction was 2:1. AF was not self-limiting, and after attempts of conversion with injections of ajmaline (50 mg) and aminodarone (300 mg) had failed, a direct-current shock of 150 J terminated the arrhythmia. Programmed atrial stimulation revealed an anterograde effective refractory period of the accessory pathway of 200 ms.

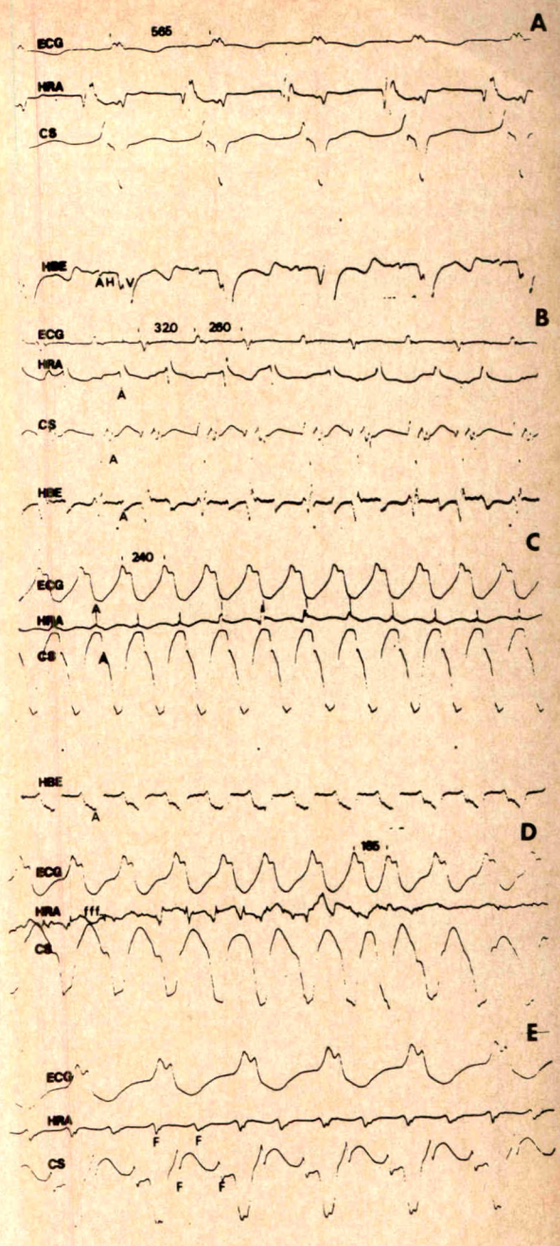

FIGURE 1. A, recordings during sinus rhythm. **B,** orthodromic tachycardia with alternating cycles of 320 and 260 ms. Note the asymmetric retrograde atrial activation sequence, suggesting a left-sided accessory pathway. **C,** antidromic tachycardia with a cycle length of 240 ms. **D,** atrial fibrillation with a fast ventricular response; the minimal R-R distance is 185 ms. **E,** atrial flutter with 2:1 atrioventricular conduction. CS = left atrial electrogram from the coronary sinus; ECG = electrocardiographic lead V_1; HBE = His bundle electrogram; HRA = high right atrial electrogram.

Chronic electrophysiologic study on subsequent days found that antidromic tachycardia was still inducible after medication with sotalol and orthodromic tachycardia after application of disopyramide and propafenone. The tachycardias could be controlled by aprindine, 100 mg daily. This drug increased the effective refractory period of the accessory pathway to 240 ms.

Although right bundle branch block in patients with Wolff-Parkinson-White syndrome has been described,[2] we cannot explain the alternation of normal conduction and incomplete right bundle branch block in our patient. The work of Cosio et al[1] and our experience suggest that a transition of antidromic tachycardia into AF is possible and probably not exceptional. AF in patients with short effective refractory periods of the accessory pathway (as found in our case), or with shortening of this period under influence of catecholamines (as described in the case of Cosio et al[1]), is life-threatening.

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1. **Cosio FG, Benson DW Jr, Anderson RW, Hession WT, Pritzker MR, Kriett JM, Benditt DG.** Onset of atrial fibrillation during antidromic tachycardia: association with sudden cardiac arrest and ventricular fibrillation in a patient with Wolff-Parkinson-White syndrome. Am J Cardiol 1982;50(Aug): 353–359.
2. **Castillo CA, Castellanos A, Befeler B, Myerburg RJ, Agha AS, Vagueiro MC.** Arrival of excitation at right ventricular apical endocardium in Wolff-Parkinson-White syndrome type A, with and without right bundle-branch block. Br Heart J 1973;35:594–600.

IMPORT OF EXERCISE-INDUCED VENTRICULAR ARRHYTHMIA IN MALIGNANT VENTRICULAR ARRHYTHMIA

Weaver et al[1] detail an experience with survivors of out-of-hospital cardiac arrest undergoing exercise testing. The landmark work by this group in defining this complex patient population remains unparalleled. There is a fundamental methodologic flaw, however, in these current data which limit conclusions regarding the import of exertionally induced ventricular arrhythmia (VA). The exercise testing protocol did not include *continuous recording* of all rhythm to allow true quantification of the density or complexity of ventricular premature beats (VPB). Rather, rhythm was "monitored continuously by the oscilloscope and recorded each minute." Several years ago we addressed the issue of continuous recording of rhythm versus intermittent sampling and found an 18% increase in coded VPB during continuous recordings but, more importantly, a 6-fold increase in the disclosure of complex and repetitive VPB (56 versus 9 episodes).[2] Second, the indication for termination of exercise by Weaver et al was increasing VA. Thus, the prognostic weight of those forms of VPB (repetitive or salvos) now considered to carry highest risk[3] cannot be assessed in the current report.

Our experience with a similar population is considerably different. The indications for terminating exercise in our laboratory is provocation of salvos of ventricular tachycardia (VT). Thus, 65% of our patients with a history of malignant VA exhibit VT salvos and 91%, ventricular couplets.[4] Patients with malignant VA who continue to exhibit VT salvos during exercise despite control of arrhythmia during extended electrocardiographic recordings remain at extreme risk for sudden death or recurrence. Abolition of these forms of VPB with antiarrhythmic drugs, however, results in enhanced long-term survival.[4]

Thomas B. Graboys, MD
Boston, Massachusetts

1. **Weaver WD, Cobb LA, Hallstrom AP.** Characteristics of survivors of exertion- and nonexertion-related cardiac arrest: value of subsequent exercise testing. Am J Cardiol 1982;50(Oct):671–676.
2. **Antman E. Graboys TB, Lown B.** Continuous monitoring for ventricular arrhythmia during exercise tests. JAMA 1979;26:2802.
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4. **Graboys TB, Lown B, Podrid PJ, DeSilva R.** Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. Am J Cardiol 1982; 50:437–443.

REPLY: We agree that the qualitative and quantitative assessment of complex VA during exercise testing can be enhanced by continuous monitoring during the test. Although we did not report the results, continuous recording of the electrocardiogram on magnetic tape during and after exercise was accomplished in all but 3 of the 90 patients in our report. With continuous monitoring we detected only 5 additional (6%) patients (total 49%) with any complex VA. In 10% of patients, the physician missed repetitive forms present on the magnetic tapes. The forms of arrhythmias documented by either the physician or by the continuous recordings were not of prognostic value in subsequent determinations of survival. Therefore, in assessing outcome in this group of patients, only exercise-evoked angina or failure to augment systolic blood pressure were of prognostic importance. Exercise testing was most often patient-limited because of complaints of fatigue and not because of arrhythmias.

Graboy's patients and ours have both experienced recurrent serious arrhythmias. We believe that the patients followed by our group, that is, survivors of out-of-hospital ventricular fibrillation, may differ from patients referred for management of recurrent symptomatic VT. Few of our patients exhibit paroxysms of symptomatic VT during follow-up. We do not know if sustained VT preceded the episodes of cardiac arrest in patients treated by our emergency care system; however, we suspect that was not usual. Sustained VT has rarely been recorded at the time these patients are initially assessed by the paramedical personnel, and most patients had no apparent symptoms immediately before collapse. It is, of course, quite likely that ventricular fibrillation was preceded by a few beats of rapid VT. In survivors of out-of-hospital ventricular fibrillation, VT is relatively uncommon during exercise testing as well as 24-hour ambulatory electrocardiographic recording.[1] On the other hand, rates of 65 to 90% have been repeated in patients with malignant symptomatic arrhythmias.[2,3] The former group more commonly stops exercise with symptoms of left ventricular dysfunction, while the latter stops because of arrhythmias. Because of the infrequent occurrence of VT during ambulatory monitoring (10%) and exercise testing (8%), these tests appear to be of limited use and offer guidelines to treatment in only a few of our previously resuscitated patients.

Although both groups of patients share many common characteristics, differences in ambient arrhythmias, in the syndromes associated with arrhythmias, and perhaps also in the arrhythmias immediately preceding VF all suggest that one should be cautious in lumping the syndromes of symptomatic VT and out-of-hospital ventricular fibrillation—treatment strategies and efficacy may differ for the groups.

W. Douglas Weaver, MD
Leonard A. Cobb, MD
Alfred P. Hallstrom, PhD
Seattle, Washington

1. **Weaver WD, Cobb LA, Hallstrom AP.** Ambulatory arrhythmias in resuscitated victims of cardiac arrest. Circulation 1982;66:212.
2. **Graboys TB, Lown B, Podrid PJ, DeSilva R.** Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. Am J Cardiol 1982; 50:437–443.
3. **Graboys TB, Lampert S, Lown B.** Yield of ventricular arrhythmia during exercise testing in patients with prior cardiac arrest. Circulation 1982;Suppl II:II-27.

APICAL HYPERTROPHIC CARDIOMYOPATHY

We read with interest the article by Maron et al,[1] and wish to point out certain additional differences between their cases and the Japanese form of apical hypertrophic cardiomyopathy (HC).[2–4] The latter is found predominantly in males and the prognosis seems to be better than in the usual HC. In addition to the mentioned differences in the degree of T-wave negativity, the QRS axis lies between 0° and +90°.[2,3] Septal Q waves are often lacking, as found in 83% of Yamaguchi's patients and in the 2 cases reported outside Japan.[3,4] Neither QRS axis nor septal Q waves was commented on by the authors.[1] Spatial vectorcardiograms in our case and in those reported from Japan disclosed a QRS loop oriented to the left and inferiorly with characteristically elongated T-loops oriented to the right and posteriorly.[2,3] Are these additional electrocardiographic and vectorcardiographic findings available for comparison? The spade-like angiographic appearance is very different from that seen in Maron's cases, and we suggest that the term "apical hypertrophic cardiomyopathy" should be reserved for the Japanese form[2–4] which shows marked concentric apical hypertrophy rather than the apical distribution of septal hypertrophy with mid-ventricular constriction.[1]

Edward G. Abinader, FRCPI
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1. **Maron BJ, Bonow RO, Seshagiri TN, Roberts WC, Epstein SE.** Hypertrophic cardiomyopathy with ventricular septal hypertrophy localized to apical region of left ventricle (apical hypertrophic cardiomyopathy). Am J Cardiol 1982;49(June):1838–1848.
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REPLY: Abinader raises an important consideration related to the morphology and nomenclature of HC. The application of 2-dimensional echocardiography to the study of patients with HC has demonstrated that a diverse spectrum of patterns of left ventricular (LV) hypertrophy may occur.[1,2] One pattern is characterized by disproportionate hypertrophy in the LV apical region (see References 1 to 4 in Abinader's letter). This morphologic form of HC appears quite common in Japan (see Reference 2 in Abinader's letter), where it is associated with a distinctive electrocardiographic pattern ("giant T-wave inversion") and a "spade-like" LV angiographic appearance. In our report, we described a subgroup of patients with HC who had a distribution of LV hypertrophy which was similar (but perhaps not identical) to that described by the Japanese investigators. Our patients also differed somewhat with regard to the LV angiographic appearance and electrocardiographic pattern.

From a morphologic point of view, however, the differences in distribution of LV hypertrophy exhibited by those patients with "apical hypertrophic cardiomyopathy" reported from several centers (including those in Japan) appear to constitute relatively minor anatomic variations. Differences in the LV angiographic appearance probably only reflect the variations in distribution of hypertrophy. In each patient with apical HC, the common morphologic denominator was hypertrophy confined to, or located primarily in, the LV apical region.

Because a great number of patterns of LV hypertrophy and morphologic subsets may be identified in HC (many of which have different clinical or electrocardiographic features[3]), I would not favor applying a different official name or label to each of these individual variations. Perhaps it would be preferable to refer to the subset of patients reported from Japan as "apical hypertrophic cardiomyopathy of the Japanese type" and other closely related variants simply as "apical hypertrophic cardiomyopathy" or, alternatively, "hypertrophic cardiomyopathy with distally located LV hypertrophy."

Barry J. Maron, MD
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1. **Maron BJ, Gottdiener JS, Epstein SE.** Patterns and significance of the distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide-angle, two-dimensional echocardiographic study of 125 patients. Am J Cardiol 1981;48:418–428.
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VENTRICULAR ACTIVATION TIME WITH LEFT VENTRICULAR HYPERTROPHY

Toyoshima et al[1] demonstrated a significant correlation between transmural conduction index and ventricular septal (VS) thickness, and that the transmural conduction index was significantly greater in the group with than in the group without left ventricular (LV) hypertrophy. There was no significant difference, however, between mean ventricular activation time in lead V_5 in these 2 groups. According to the authors' findings, LV activation time is not related to VS thickness.

In a recent study[2] performed by us, we obtained results which differ from those of Toyoshima et al on the latter point. We studied the correlation between electrocardiographic, vectorcardiographic, and echocardiographic parameters in 92 patients with and without LV hypertrophy. The ventricular activation time, which was taken in lead V_5 and orthogonal Franks' leads X, Y, and Z, was significantly ($p < 0.01$) greater in the presence of LV hypertrophy. There was a statistically significant correlation between ventricular activation time in lead V_5 and posterior wall thickness ($r = 0.41$, $p < 0.03$) in the group with concentric LV hypertrophy. In this group, posterior wall thickness (mean 12 ± 3 mm) also correlated well with the ventricular activation time in lead Z ($r = 0.84$, $p < 0.01$), while the correlation coefficient between VS thickness and ventricular activation time in lead Z was 0.53 ($p < 0.05$).

In the group with eccentric hypertrophy (aortic regurgitation), we found no correlation between ventricular activation time in lead V_5 and posterior wall or septal thickness, while there was a very good correlation between posterior wall thickness and ventricular activation time in lead Y ($r = 0.92$, $p < 0.004$).

Our observations on ventricular activation time in LV hypertrophy, especially when orthogonal leads are used, thus contradict the findings of Toyoshima et al[1] that ventricular activation time is not related to LV thickness, and are partly in agreement with data reported by Carter and Estes.[3]

In spite of technical limitations in measuring ventricular activation time in lead V_5 (which was recorded at a speed of 25 mm/s while the orthogonal leads were recorded at 100 or 250 mm/s), we believed that ventricular activation time increased in patients with LV hypertrophy and that there is a linear correlation between ventricular thickness and ventricular activation time.

Ilya A. Ovsyshcher, MD, PhD
Kenneth L. Wanderman, MD
Moshe Gueron, MD
Beer-Sheba, Israel

1. **Toyoshima H, Park Y, Ishikawa Y, Nagata S, Hirata Y, Sakakibara H, Shimomura K, Nakayama R.** Effect of ventricular hypertrophy on conduction velocity of activation front in the ventricular myocardium. Am J Cardiol 1982;49(June):1938–1945.
2. **Ovsyshcher I, Gueron M, Wanderman K, Gussarsky Y.** The relationship between echocardiographic parameters and the magnitude of cardiac electrical potentials. IX World Congress of Cardiology, Moscow, 1982;1:713.
3. **Carter WA, Estes EH Jr.** Electrocardiographic manifestations of ventricular hypertrophy: a computer study of ECG-anatomic correlations in 319 cases. Am Heart J 1964;68:173–182.

REPLY: I appreciate the interest of Ovsyshcher et al in our article on LV hypertrophy and conduction velocity. Although they state that their observations on ventricular activation time in LV hypertrophy contradict ours, we disagree.

The beginning of the intrinsicoid deflection or so-called ventricular activation time is originally applied to the semidirect unipolar lead electrocardiogram, such as precordial lead one, and has been considered to closely approximate the time when the activation front arrives at the ventricular subepicardial site beneath the electrode in problem. Debates remain as to its exact timing and accuracy.[1,2] In the indirect bipolar lead electrocardiograms, such as the standard bipolar limb lead and orthogonal lead, however, there should be no time phase equivalent to ventricular activation time in precordial lead 1 in terms of arrival of activation front at the specific site. Thus, I have no comment on their observations as to "ventricular activation time in the orthogonal lead electrocardiograms" versus ventricular hypertrophy.

Ovsyshcher et al found low but significant correlation ($r = 0.41$, $p < 0.03$) between ventricular activation time in lead V_5 and posterior wall thickness in the group with concentric LV hypertrophy, while we found no statistically significant difference in the mean ventricular activation time in lead V_5 in the groups with and without LV hypertrophy. This apparent contradiction may be due to selection of materials, their technical inadequacy in recording and measuring electrocardiograms, or both. In our study[3] of 47 patients with systemic hypertension, aortic valvular disease, or dilated cardiomyopathy without any apparent conduction disturbance, we have found no significant difference in the mean ventricular activation time in lead V_5 in the groups with and without LV hypertrophy and no significant correlation between VS thickness and ventricular activation time in the total group of hearts, similar to the findings in our previous report. When patients who had congestive heart failure (usually from dilated cardiomyopathy) were excluded, a low but significant ($r = 0.42$, $p < 0.025$, $n = 40$) linear correlation between the 2 variables was observed, as in the letter by Ovsyshcher et al. However, the difference in mean ventricular activation time was still insignificant in the groups with and without LV hypertrophy (45.93 ± 6.52 ms versus 42.89 ± 6.76, $p > 0.10$). Thus, the selection of patients seems to be a key point that yielded different results.

As long as LV hypertrophy is defined by only ventricular wall thickness, we are of the opinion that there is no correlation with ventricular activation time, because any heart with any pathologic condition should be included in both control and hypertrophied groups for analysis.

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1. **Sodi-Pallares D, Barbato E, Delmar A.** Relationship between the intrinsic deflection and subepicardial activation: an experimental study. Am Heart J 1950;39: 387–396.
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POLYMORPHOUS VENTRICULAR TACHYCARDIA

In a recent report Soffer et al[1] discussed torsade de pointes arrhythmias. In their Table I they listed "conditions in which torsade de pointes in association with Q-T interval prolongation has been described." In this table the authors mentioned that mitral valve prolapse might be a cause of torsade de pointes. Recently, Bennet[2] described the first well-documented case of torsade de pointes

in a patient with mitral valve prolapse. We observed a similar case.

A 54-year-old woman was admitted when an electrocardiogram (ECG) disclosed multiple premature ventricular beats and several runs of ventricular tachycardia (Fig. 1). The Q-T interval was 0.52 to 0.56 second (upper limit 0.40 second), and bizarre, inverted T waves in all leads were found (Fig. 1). Three days of therapy, which included lidocaine, propranolol, and atropine, failed to prevent recurrences of the arrhythmia (>60 episodes of torsade de pointes). Ventricular arrhythmia disappeared after infusion of isoproterenol (2 mg/500 ml of 5% glucose). After 48 hours, the ECG returned to normal. Physical examination revealed an apical grade 2/6 late systolic murmur and an echocardiogram showed mitral valve prolapse.

Several drugs, poisons, and diseases should also be added to their Table I: ajmaline,[3] lidocaine,[4] haloperidol,[4] suxamethonium,[5] arsenic[6] and strychnine intoxication (our unpublished data), scorpion venom,[7] cardiomyopathy,[8] myotonic dystrophy,[9] osteogenic sarcoma,[10] carcinoma of the lung (our unpublished data), and hypothermia.[11]

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1. **Soffer J, Dreifus LS, Michelson EL.** Polymorphous ventricular tachycardia associated with normal and long Q-T intervals. Am J Cardiol 1982;49:2021–2029.
2. **Bennett KR.** Torsade de pointes and mitral valve prolapse [letter]. Am J Cardiol 1980;45:715.
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10. **Seibert KA, Rettenmier CW, Waller BF, Battle WE, Levine AS, Roberts WC.** Osteogenic sarcoma metastatic to the heart. Am J Med 1982;73:136–141.
11. **Emslie-Smith D, Hadden GE, Stirling GR.** The significance of changes in the electrocardiogram in hypothermia. Br Heart J 1959;21:343–351.

ABNORMAL ELECTROCARDIOGRAMS IN HIGHLY TRAINED ATHLETES

The report by Oakley and Oakley[1] raises a question concerning the specific criteria for abnormal septal hypertrophy, particularly in the context of an athletic individual. Athlete 4, for example, had both electrocardiographic evidence of left ventricular hypertrophy with strain and an echocardiographic septal-free wall ratio of 1.9:1. It is unclear how the diagnosis of nonobstructive cardiomyopathy was excluded in this patient. The authors appear to emphasize a normal exercise response as an important differential point. Normalization of electrocardiographic abnormalities with increasing heart rates has been reported in hypertrophic cardiomyopathy.[2] Good exercise capacity is not inconsistent with the diagnosis of hypertrophic cardiomyopathy. The specificity and sensitivity of the commonly used features of asymmetric septal hypertrophy are still debated.[3] Three questions remain: (1) How was hypertrophic cardiomyopathy excluded in patient 4? (2) Can physiologic exercise induce extreme septal hypertrophy, and to what degree? (3) Does exercise-induced hypertrophy predispose to the complications seen in familial hypertrophic cardiomyopathy?

Michael H. Goldman, MAJ, MC
Bruce E. Dunn, COL, MC
Washington, D.C.

1. **Oakley DG, Oakley CM.** Significance of abnormal electrocardiograms in highly trained atheletes. Am J Cardiol 1982;50 (Nov):985–989.
2. **Cosio FG, Moro C, Alonso M, De la Calzada CS, Llovet A.** The Q waves of hypertrophic cardiomyopathy: an electrophysiologic study. N Engl J Med 1980;302:96–99.
3. **Maron BJ, Epstein SE.** Hypertrophic cardiomyopathy: recent observations regarding the specificity of three hallmarks of the disease: asymmetric septal hypertrophy, septal disorganization and systolic anterior motion of the anterior mitral leaflet. Am J Cardiol 1980;45: 141–154.

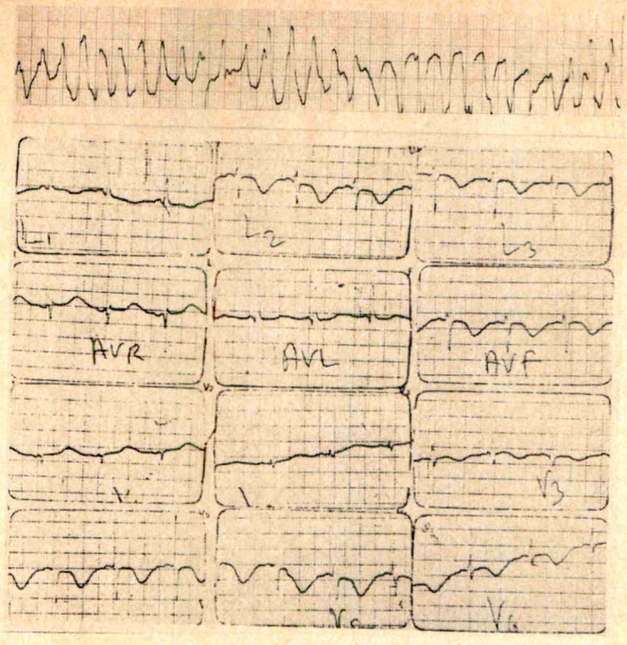

FIGURE 1. Top, a continuous strip recorded in monitoring lead, showing a sustained episode of ventricular tachycardia characteristic of torsade de pointes. **Bottom,** 12-lead electrocardiogram: sinus rhythm of 75 beats/min, broad, inverted T waves in leads I, II, III, aVR, aVF, V_3-V_6, and a markedly prolonged Q-T interval (0.52 to 0.56 second) can be seen.

REPLY: We are grateful to Goldman and Dunn for highlighting some important issues raised in our report. They correctly identified the 1 patient (patient 4) who gave rise to the most diagnostic difficulties.

With regard to the exercise test results, they quote Cosio et al. These investigators did not exercise patients with hypertrophic cardiomyopathy; they used atrial pacing and atrial extrastimulus testing during a supine electrophysiologic study—a completely different stress! We accept that normalization of the exercise electrocardiogram does not exclude disease, but we are unaware of any report showing such normalization of ST-T wave abnormalities in patients with hypertrophic cardiomyopathy during exercise. Our own studies have never shown this.

Coming to the 3 questions, number 1 should read "How could hypertrophic cardiomyopathy in patient 4 be *proven*?" It is surely up to the physician to prove that his patient is sick rather than the patient to prove that he is not. This is especially relevant when the patient's way of life depends upon supreme physical fitness. The answer to question 2 is unknown. Only a longitudinal study documenting the appearance of asymmetric hypertrophy as training progresses could establish whether it can be training-induced, and such a study would not distinguish between physiologic adaptation and exercise-induced disease in predisposed subjects. If such changes are adaptive, then a degree of resolution might be expected if training is stopped. We quoted a patient in whom this was so. Question 3 will only be answered by following up these patients who have been given the real benefit of any doubt that some still feel. So far all our patients are well, in training, and asymptomatic.

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Celia M. Oakley, MD, FRCP
London, England

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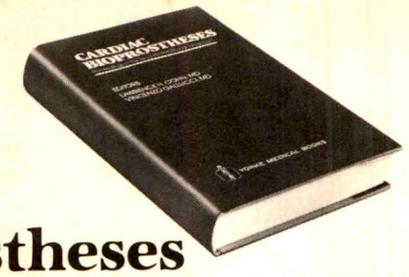

Cardiac Bioprostheses

Proceedings of the Second International Symposium
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edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
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Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

HOW SUPPLIED
Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

0.15 mg (1/400 grain):
N 0071-0568-24—Bottle of 100 tablets;
N 0071-0568-13—Convenience Package.

0.3 mg (1/200 grain):
N 0071-0569-24—Bottle of 100 tablets;
N 0071-0569-13—Convenience Package.

0.4 mg (1/150 grain):
N 0071-0570-24—Bottle of 100 tablets;
N 0071-0570-13—Convenience Package.

0.6 mg (1/100 grain):
N 0071-0571-24—Bottle of 100 tablets;
N 0071-0571-13—Convenience Package.

0568G060

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Morris Plains, NJ 07950

NATURE
HAS A WAY
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So does NITROSTAT®
(nitroglycerin tablets, USP)

Just by the way it's made, NITROSTAT, too, has built-in protection—protection against loss of nitroglycerin. In fact, NITROSTAT is more stable than conventional nitroglycerin tablets under all conditions of temperature and humidity tested.

But that's not all. Average assay still shows better than 100% of label claim for at least 60 months after manufacture of NITROSTAT. Because of this stability NITROSTAT has a five-year expiration date.*

What's more, only NITROSTAT Tablets are available in convenient packages of 4 x 25 tablets. So emergency angina relief can be ready when needed in four different locations. "Because of its rapid action, long-established efficacy and low cost, nitroglycerin is the most useful drug among the organic nitrates that can be given sublingually."[1] NITROSTAT...useful alone or as concomitant therapy with long-acting nitrates or propranolol.

*Five-year expiration date when stored at recommended storage conditions in an unopened bottle. Data on file, Medical Affairs Dept, Parke-Davis.

REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

Please see preceding page for brief summary of prescribing information.

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25th Anniversary

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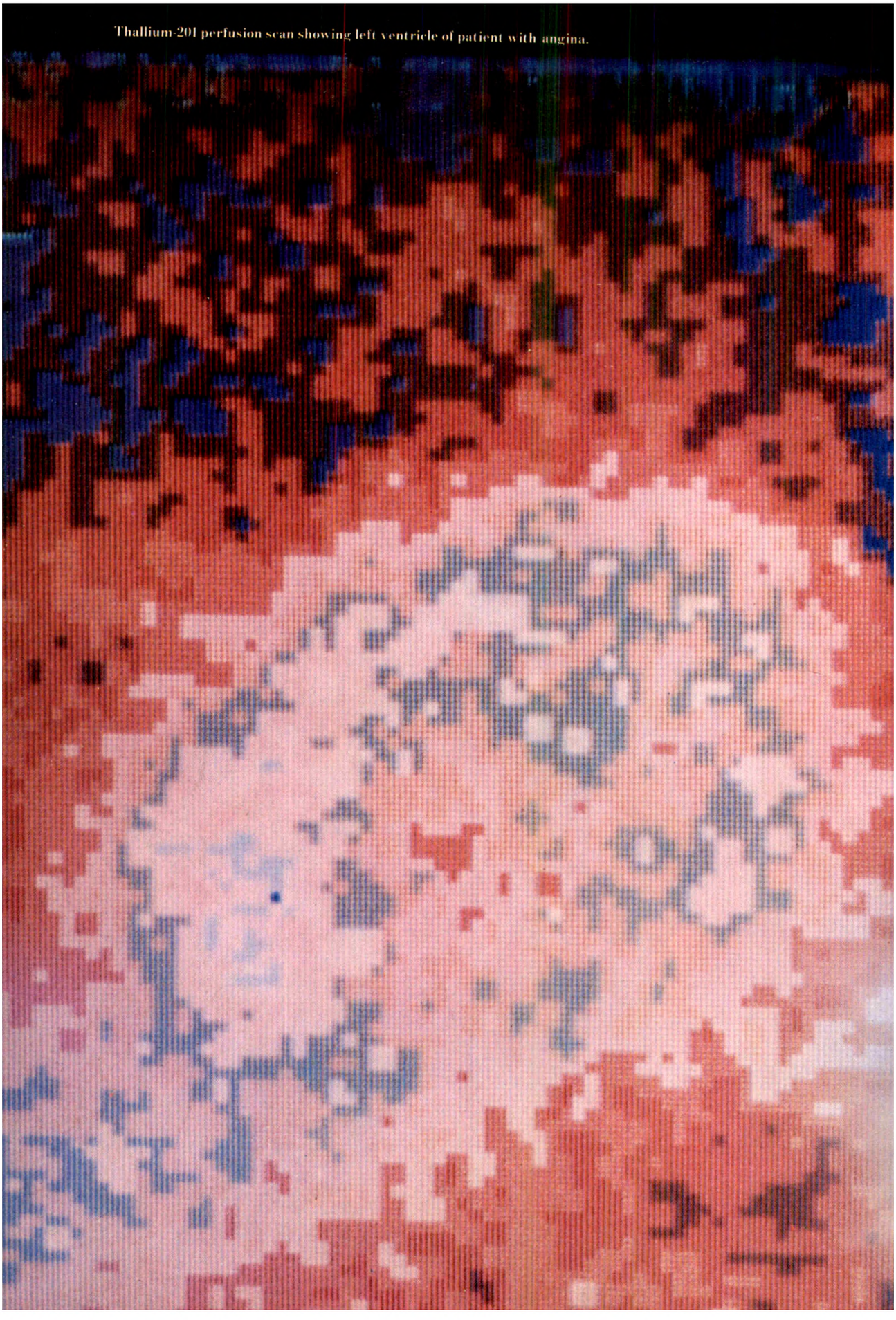
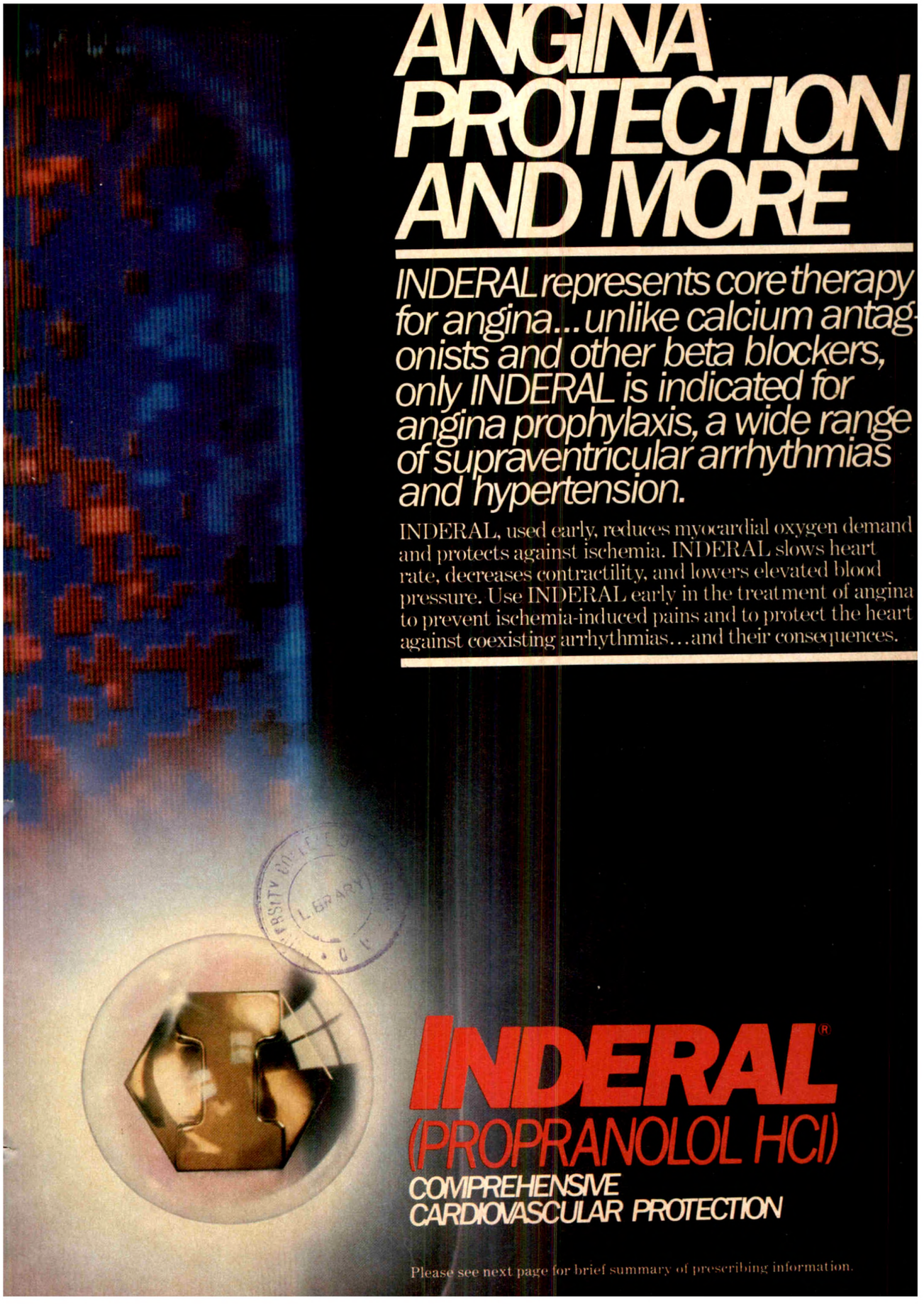


Thallium-201 perfusion scan showing left ventricle of patient with angina.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COMPREHENSIVE
CARDIOVASCULAR PROTECTION
Please see next page for brief summary of prescribing information.

INDERAL®
(PROPRANOLOL HCl)

CORE THERAPY FOR ANGINA.

TM

The appearance of these tablets is a trademark of Ayerst Laboratories.

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

Propranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains **10 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains **20 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains **40 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

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The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

Ayerst®

AYERST LABORATORIES
New York, N.Y. 10017

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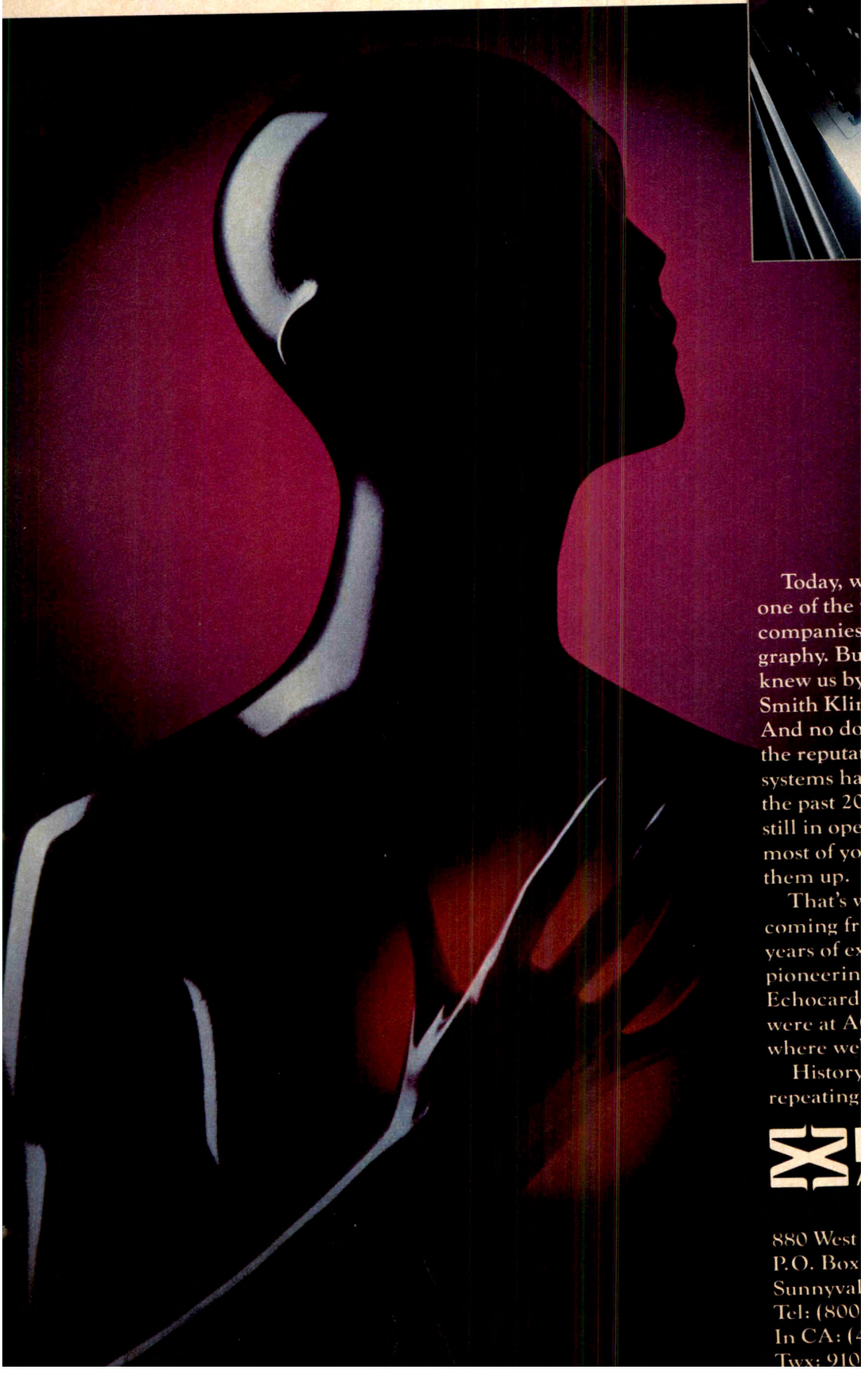

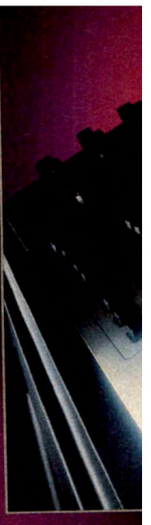

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

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Carolina, P.R. 00630

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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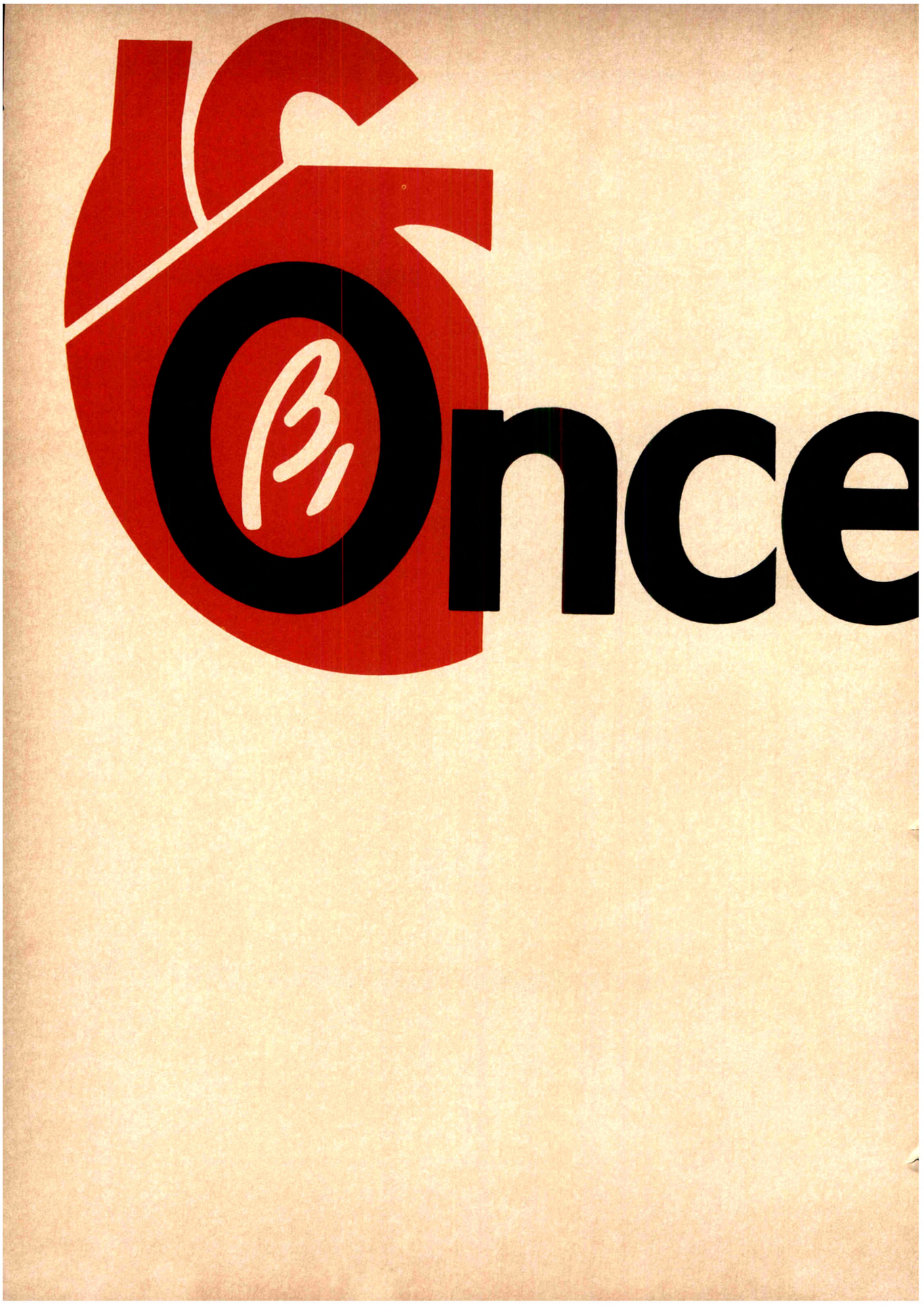
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New dosage schedule: To start, 100 mg once-a-day, or in divided doses.

Lower doses (especially 100 mg) may not maintain full effect at end of 24-hour period. Measure BP near end of dosing interval, adjust to larger or more frequent dosage if needed.

*exerts a relative preference for beta-one receptors; this preference is not absolute.

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please turn page for brief Prescribing Information.

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Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Prescribing Information

Brief Summary of Prescribing Information.

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

C83-16 (Rev. 5/83)

536-5761-A

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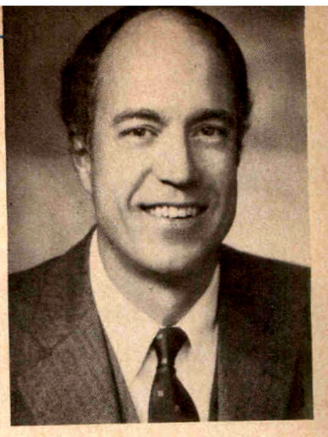

Changes in The AJC Since June 1982

This piece will describe certain visible and nonvisible changes in the AJC during the first 12 months (since June 1982) of the present editorship.

1. Alteration of the *Instructions-to-Authors* page came first. This page is an extremely important one and I encourage all authors submitting manuscripts to the AJC to read these Instructions carefully before the final typing of their manuscripts. I include a reprint of the Instructions page when returning a manuscript to an author requesting revision of his or her manuscript. In addition to the required stylistic changes delineated in the Instructions, authors are encouraged, as stated in this page, to suggest 1 or more nonlocal potentially objective reviewers and also potentially biased reviewers for their manuscripts. These suggestions have been quite useful to me, and, I hope, to the authors. I generally send a manuscript to 1 reviewer suggested by the authors and to 1 reviewer of my choosing. I never send a manuscript to a potentially biased reviewer if so requested by an author. The Instructions page also describes the method of having a manuscript reviewed blindly. This method of review is available to the submitting authors on request and this request is always honored by the editor.

2. The next change made was on the *Editorial Board* page. The board members were separated according to subspeciality.

3. The format of the *Title Page* was changed in October 1982 to make the content of this page more compact and the layout more attractive. Initially, both the title and authors' names were "flush left" but now each is centered.

4. The style and type size of the *References* was changed in October 1982. Although all authors as well as inclusive pages are now listed, the space occupied by each reference is considerably less than previously.

5. The *Table of Contents* page was changed in January 1982. The articles are now grouped by the various disease categories—Coronary, Valvular, Myocardial, Congenital, Arrhythmias and Conduction Disturbances, Systemic Hypertension, Congestive Heart Failure, etc. Exceptions to these categories include Methods, Cardiac Pharmacology, Experimental Studies, Brief Reports, Editorials, Point of View, Historical Studies, Letters, and The AJC 25 Years Ago.

6. The bottom half of the *Cover* was changed in January 1983 to include the general categories of the table of contents.

7. The Letters to the Editor were retitled simply *Letters* and in March 1983 they were laid out in 3-column rather than 2-column format to add variation. The layout of this section was made more compact, and a request was inserted on the initial "letter page" of each issue indicating that a letter concerning an article published in the AJC must be received from USA readers within 2 months of the article's publication.

8. A *Brief Report* section was added in September 1982. These are primarily single case reports and they now average about 1.4 printed pages apiece, including figures.

9. The *Point-of-View* section was added in March 1983. This section is intended to provide a medium for brief presentation of a concept or idea. The idea may or may not be provable and references are not required. The section may be considered in the category of a "capsule editorial." The editorial, in contrast, is a well-developed thesis.

10. *Quotations*, inserted on empty spaces of pages at the end of individual articles, began appearing in February 1983. These will focus primarily, but not entirely, on scientific matters. I would be pleased to receive quotations from any reader and if the quotation appears, appropriate credit will be given to the submitter.

Continued on page A10

11. The *From-the-Editor* page began in July 1982, initially to emphasize some items described in the Instructions to Authors page, and has continued with discussions of the manuscript review process, relations between authors, editors, reviewers, publishers, and advertisers, and viewpoints on various portions of a manuscript. It is my intent to continue these columns for awhile.

12. A new section entitled "The AJC 25 Years Ago" was added in May 1983 and will be a monthly feature hereafter.

As the foregoing changes were being implemented, a number of other changes also were taking place. A strenuous attempt has been made to make each manuscript more compact so that there is more content per page for the reader without an increase in the *Journal*'s size or price. During this first year, the average content per page has increased by slightly over 20%. The means by which this increased content per page was made possible are the following: (1) The title page is more compact. (2) The references are smaller than previously, and in recent months, fewer in number. (3) More figures and tables occupy only a half column rather than portions of 2 columns. (4) Less space is now (last 2 months only) retained between figures and/or tables and the text. (5) An additional line in each column was acquired by deleting the Journal's title at the bottom of each page. (6) The use of abbreviations, numbers (<10 as well as >10) and symbols has saved many lines per page. I prefer no more than 3 abbreviations per manuscript and that they be limited to commonly recognized cardiologic terms, preferably those appearing in the article's title. The symbols for percent (%), less than (<) and greater than (>) save space and decrease reading time. It takes 36 spaces to spell out the first 9 numbers (1 to 9), but only 9 spaces are utilized when numbers are used, a 4-fold savings of space.

Moreover, the publisher is providing more pages per issue than a year ago. Comparison of 4 items in the last 2 months of the previous editorship (May to June 1982) with the 2 latest months (before this piece went to press) under the present editorship is illustrated in the table. The number of articles published between these 2 periods increased 52% while the number of pages published increased only 8%. The average number of pages per article decreased 29%. Although the number of lines per page (2 columns per page) increased by nearly 2%, the utilization of a single additional line per page potentially provides 4 additional full pages per issue and 48 additional pages per year.

COMPARISON OF MAY-JUNE 1982 AJC TO FEBRUARY-MARCH 1, 1983 AJC

	Combined 5/82 + 6/82	Combined 2/83 + 3/83	Percent Change
Number of papers	64	97	+52
Average number of pages per paper	7.5	5.3	−29
Number of pages	480	519	+ 8
Number of lines per column	61	62	+ 2

In addition to the visible changes made in the *Journal* in the past 12 months, several visible changes have been made in the processing of manuscripts: (1) The *reviewer forms* have been changed so that 1 entire page is for "confidential comments to the editor" and another for "comments to the authors." The editor has requested all reviewers to answer the following question on the "confidential" page: "Would you grant the editor permission to make the authors aware of who reviewed their manuscript?" (2) All manuscripts now are sent to reviewers in thick blue-and-white *container folders* which help in the organization of the text, figures, tables, and review forms. (3) New blue-and-white *mailing envelopes* have been provided. (4) *Personal letters* from the editor now accompany all manuscripts returned to authors and to nonboard reviewers when requesting a review.

The intent of most of these changes in the *Journal* is to increase content per page and this translates into increased content per issue. Suggestions for further improvements to the *Journal* are always welcomed by the editor.

William C. Roberts, MD
Editor-in-Chief

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Please see next page for a brief summary of prescribing information.

*Fischer, R.G., Compliance-Oriented Prescribing: Simplifying Drug Regimens, J. Fam. Pract. *10*:427-435 (March) 1980.

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Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus. Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg/kg) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg/kg) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Reversible hyperchloremic metabolic acidosis may occur in some patients with decompensated hepatic cirrhosis. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist. Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in sympathectomized patients. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia. Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions: *Associated with spironolactone*: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. *Associated with thiazides*: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness. Adverse reactions are usually reversible upon discontinuation of Aldactazide.

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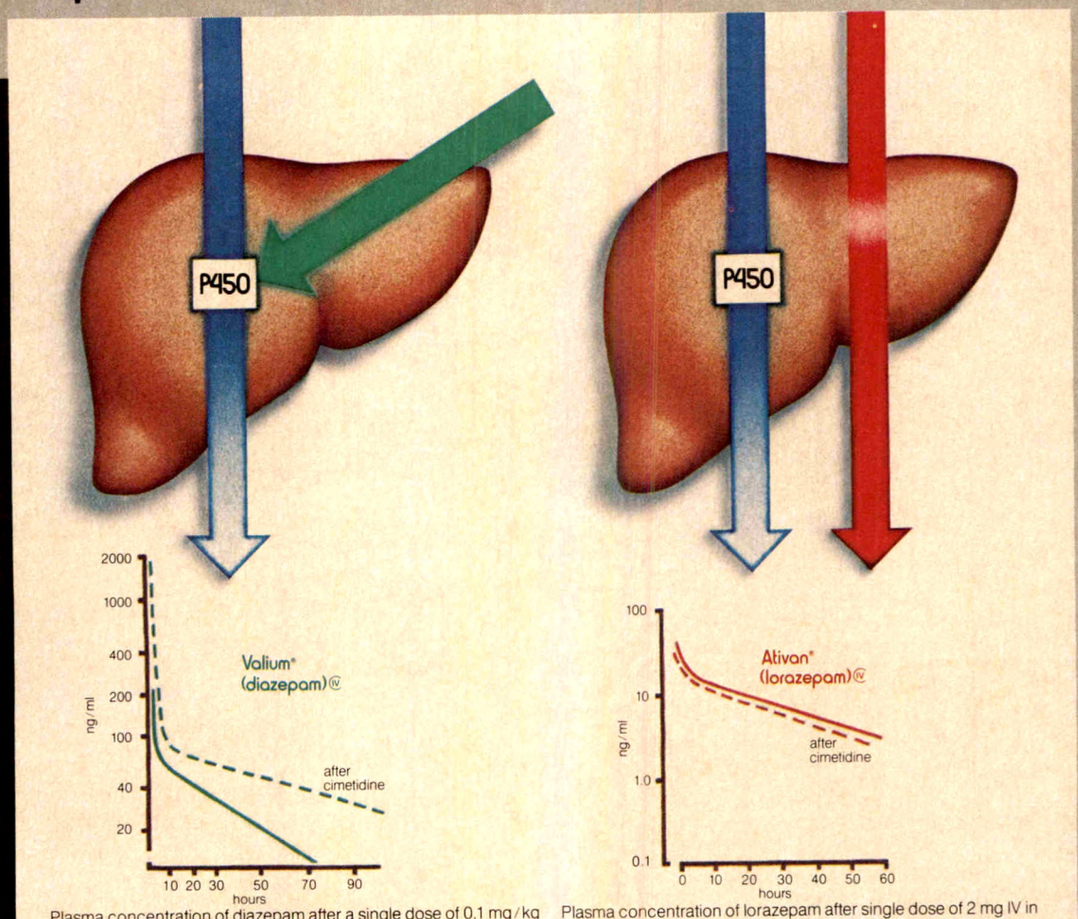
Ativan®: Agent of Change
(lorazepam)



Plasma concentration of diazepam after a single dose of 0.1 mg/kg IV to a single subject administered before (—) and after (---) pretreatment with cimetidine—5 X 200 mg orally q6h. (Adapted from Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.)

Plasma concentration of lorazepam after single dose of 2 mg IV in 8 normal subjects before (—) and after (---) 7 days of treatment with cimetidine, 300 mg orally qid. (Adapted from Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.)

because it doesn't utilize the P450 system

All drugs inactivated by oxidative metabolism, including cimetidine and most benzodiazepines, utilize the cytochrome P450 oxidase enzyme system and, therefore, compete for it when given concomitantly. Patients on cimetidine, for example, are apt to experience excessive drowsiness when taking a benzodiazepine dependent on this system—because benzodiazepine clearance is delayed and plasma levels increase.

Ativan® (lorazepam) is inactivated by simple, one-step glucuronidation and is not subject to N-dealkylation or hydroxylation by the P450 system—unlike diazepam, chlordiazepoxide, clorazepate and prazepam, all CIV.

And, since Ativan does not compete for the P450 system, its elimination is not appreciably affected by concomitant use of cimetidine... one more reason why Ativan is becoming the anxiolytic of choice for an increasing number of physicians.

See important information on following page.

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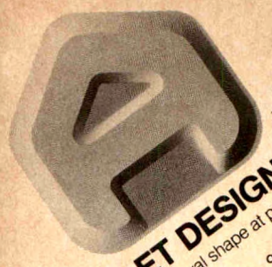
Ativan®
for (lorazepam)ⓥ
Anxiety



The appearance of these tablets is a trademark of Wyeth Laboratories.

NEW TABLET DESIGN 0.5 mg and 1 mg

(2 mg tablet retains original oval shape at present)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

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DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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VOLUME 51

NUMBER 10

CONTENTS

CORONARY HEART DISEASE

1573 Intracoronary Thrombolysis in Acute Myocardial Infarction: An Attempt to Quantitate Its Effect by Comparison of Enzymatic Estimate of Myocardial Necrosis With Left Ventricular Ejection Fraction

FRANZ SCHWARZ, ANDREAS FAURE, HUGO KATUS, KLAUS VON OLSHAUSEN, MANFRED HOFMANN, GERHARD SCHULER, JOACHIM MANTHEY, and WOLFGANG KÜBLER

The quantity of myocardium that can be salvaged by reperfusion of acute transmural myocardial infarction (MI) was estimated. Serial analysis of serum creatine kinase activity was carried out in 41 consecutive patients with acute MI who underwent intracoronary thrombolysis. Left ventricular ejection fraction 4 weeks after successful thrombolysis correlated closely with enzymatic estimate of MI size. Patients with reperfusion within 4 hours after onset of symptoms were assembled in group A, patients with successful reperfusion after 4 hours in group A_2, and patients without reperfusion in group B. MI size was significantly reduced to one third in group A_1 but was not reduced in group A_2 when compared with group B. It is concluded that MI size may be significantly reduced by early reperfusion in acute MI.

1579 Dynamic Evaluation of Prognosis from Time-Dependent Variables in Acute Myocardial Infarction

ERLING BIRK MADSEN, PHILIP HOUGAARD, and ELIZABETH GILPIN

To evaluate the prognostic importance of time-dependent variables for endpoints other than death, a competing risk variant of the multivariate Cox model was utilized to predict the risk of 3 endpoints (death, cardiac arrest, or cardiogenic shock) up to 44 days after admission for acute myocardial infarction in 1,140 patients. The important variables were ventricular fibrillation, age, congestive heart failure, and asystole (death); congestive heart failure, ventricular premature beats, supraventricular tachycardia, extension of infarction, and age (cardiac arrest); cardiac arrest, age, congestive heart failure, previous infarction, and nodal rhythm (cardiogenic shock). With use of the regression coefficients and hazard functions for each endpoint, the model can be directly utilized to assess risk.

1584 Prevalence and Prognosis After a First Nontransmural Myocardial Infarction

SANTIAGO COLL, ANGEL CASTAÑER, GINES SANZ, EULALIA ROIG, JORGE MAGRIÑA, FRANCISCO NAVARRO-LOPEZ, and AMADEO BETRIU

Prevalence, prognosis, and coronary anatomy associated with nontransmural myocardial infarction were prospectively assessed in a series of 458 consecutive men. Cardiac catheterization was performed in 402 of the 436 survivors. The 28 patients presenting with nontransmural myocardial infarction were younger, showed lower peak creatine kinase values, higher ejection fraction, and lower prevalence of total or subtotal occlusion of the involved coronary artery than their counterparts. Long-term survival at 4 years and occurrence of nonfatal new coronary events was similar in both groups. Thus, a more aggressive management to improve survival does not appear warranted after nontransmural myocardial infarction.

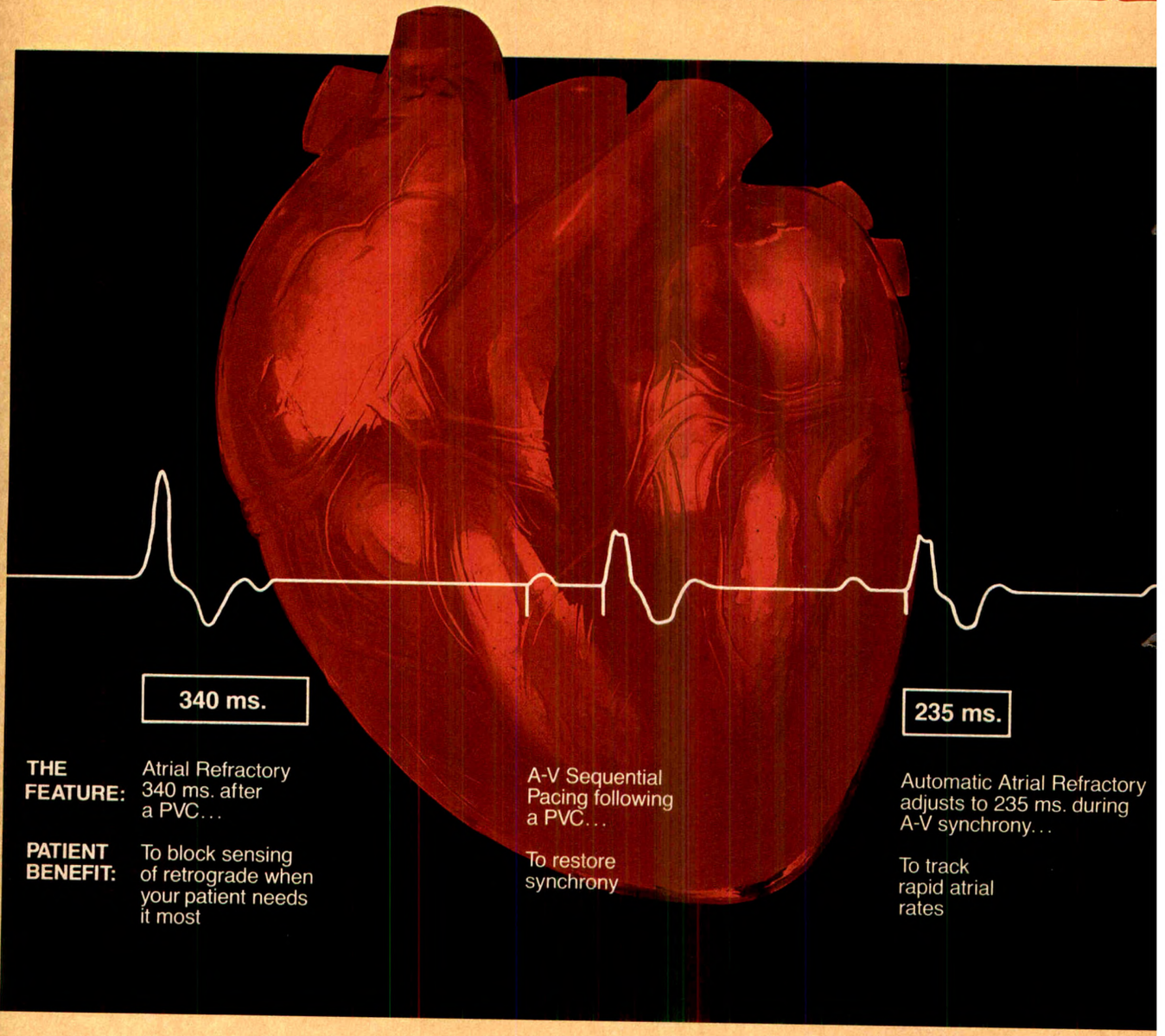
1589 Symptomatic, Electocardiographic, Metabolic, and Hemodynamic Alterations During Pacing-Induced Myocardial Ischemia

ROY V. MARKHAM, Jr., MICHAEL D. WINNIFORD, BRIAN G. FIRTH, PASCAL NICOD, GREGORY J. DEHMER, SAMUEL E. LEWIS, and L. DAVID HILLIS

Although several variables have served as markers of pacing-induced myocardial ischemia, their specificities and sensitivities are unknown. In 28 patients, atrial pacing was performed. Of the 28, 10 had no coronary artery disease. In this group, the left ventricular ejection fraction increased with pacing. Left ventricular end-diastolic pressure did not increase substantially in any of the 10, and none had myocardial lactate production. Two (20%) had transient S-T segment depression, and 4 had their usual chest pain. In the other 18 patients with coronary artery disease, atrial pacing induced a decrease in the ejection fraction and new segmental wall motion abnormalities in all. However, only 8 (44%) had an increase in end-diastolic pressure; 9 (50%) had lactate production; 10 (56%) had S-T segment depression; and 12 (67%) had their usual chest pain. Thus, the electrocardiographic, metabolic, and hemodynamic alterations that may occur during pacing-induced ischemia are specific but relatively insensitive markers of ischemia. Chest pain during pacing is a nonspecific occurrence.

Continued on page A21

New VERSATRAX II



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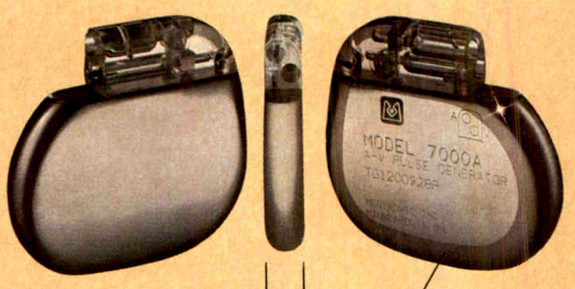

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Intended Use

The Model 7000A universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy: Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

Electrosurgical Units: Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

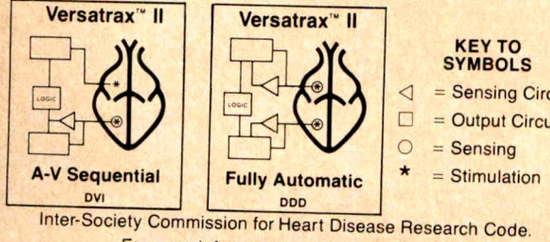
Defibrillation: Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



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1595 Effect of Oral Sustained-Release Nitroglycerin on Exercise Capacity in Angina Pectoris: Dose-Response Relation and Duration of Action During Double-Blind Crossover Randomized Acute Therapy

SERGE G. DEGRÉ, GISÈLE M. STRAPPART, JOHN C. SOBOLSKI, GUY M. BERKENBOOM, ERIC E. STOUPEL, and POL P. VANDERMOTEN

This double-blind crossover study compares the effect of 2 oral doses (2.5 and 6.5 mg) of sustained-release nitroglycerin (SRNG) on the symptom-limited exercise capacity of patients with stable exertional angina. While 2.5 mg of SRNG only increased the symptom-limited working capacity at 1 hour (+9%; $p < 0.01$), 6.5 mg SRNG was more effective at 1 hour (+25%; $p < 0.001$) and was still active at 5 hours (+27%; $p < 0.001$). Angina occurred at a higher heart rate (+5 to +8%; difference not significant and $p < 0.01$); S-T segment depression at the onset of angina was unchanged. It is concluded that 6.5 mg of orally administered SRNG is effective during at least 5 hours and that the magnitude of the benefit and its duration are dose-related.

1599 Prolonged Angina Pectoris and Persistent Negative T Waves in the Precordial Leads: Response to Atrial Pacing and to Methoxamine-Induced Hypertension

JAIME FIGUERAS, JUAN CINCA, LUIS GUTIERREZ, ROSA SEGURA, and JORGE RIUS

In 18 patients prolonged angina and persistent negative T waves in the precordial leads was associated with in-hospital spontaneous angina in 78% and myocardial infarction in 22%. Severe proximal stenosis of the left anterior descending coronary artery (LAD) was present in 14 of 16 patients with coronary arteriography. None had triple vessel disease and very few had collateral vessels. Arterial hypertension by methoxamine in 14 patients caused reversal of negative T waves without significant S-T segment shifts or lactate extraction abnormalities. Thus, prolonged angina with negative T waves in the precordial leads is almost always associated with severe LAD obstruction, 1 or 2 vessel disease, and poor collateral vessels. The nonischemic response to pacing in 55% of patients suggests that these negative T waves do not commonly represent active ischemia. Furthermore, their transient positivization may not be related to ischemia when associated with acute hypertension.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1608 Clinical Evaluation of the Internal Automatic Cardioverter-Defibrillator in Survivors of Sudden Cardiac Death

PHILIP R. REID, M. MIROWSKI, MORTON M. MOWER, EDWARD V. PLATIA, LAWRENCE S. C. GRIFFITH, LEVI WATKINS, Jr., STANLEY M. BACH, Jr., MIR IMRAN, and ANDRA THOMAS

An internal automatic cardioverter-defibrillator (IACD) was clinically evaluated in 12 patients (average age 60.6 years) who had survived an average of 3 previous cardiac arrests. Severe heart failure (NYHA class III or IV) was present in 6 patients, and the average ejection fraction was 35%. Postoperatively 1 patient had spontaneous ventricular tachycardia which was automatically converted by the IACD. Ten patients had ventricular tachycardia and 1 had ventricular fibrillation induced in the electrophysiology laboratory; there was effective conversion in all by the IACD in an average of 17.9 ± 4.2 seconds. This study suggests that (1) ventricular tachycardia, not ventricular fibrillation, is the predominant rhythm induced during programmed ventricular stimulation in these high-risk patients, and (2) the IACD effectively functions over a wide rate range of ventricular tachycardia, as well as ventricular fibrillation. The IACD appears to offer an effective method of management in a group of patients for whom no satisfactory therapy was previously available.

1614 Efficacy of Verapamil in Chronic, Recurrent Ventricular Tachycardia

JAY W. MASON, CHARLES D. SWERDLOW, and L. BRENT MITCHELL

Verapamil was administered intravenously at electrophysiologic study in 24 patients who had spontaneously recurrent and inducible ventricular tachycardia. In 7 of these patients (29%) verapamil prevented reinduction of tachycardia (5 patients) or converted sustained ventricular tachycardia to tachycardia of <5 seconds' duration (2 patients). Responders were younger and had better left ventricular function than did nonresponders. Long-term therapy with verapamil was attempted in 5 patients and was effective in 3. When not contraindicated, verapamil should be given a trial in patients whose ventricular tachycardia is unresponsive to other drugs.

1618 Electrophysiologic Effects of Lorcainide on the Accessory Pathway in the Wolff-Parkinson-White Syndrome

WOLFGANG KASPER, NORBERT TREESE, THOMAS MEINERTZ, EBERHARD JÄHNCHEN, and TIBERIUS POP

The electrophysiologic effects of the new antiarrhythmic agent lorcainide were studied in 20 patients with the Wolff-Parkinson-White syndrome. After intravenous administration of lorcainide, atrioventricular (AH), intraventricular (HV), and intramyocardial (QRS) conduction increased. Conduction over the accessory pathway was

Continued on page A25

for many post-MI patients...

Cardio-protective.

Cardioprotective is a word you won't find in standard medical dictionaries.

But you will find it appearing in the medical literature. And you will be hearing it in medical discussions. Until dictionaries recognize the term, MSD invites you to use this as a working definition of *cardioprotective:*

"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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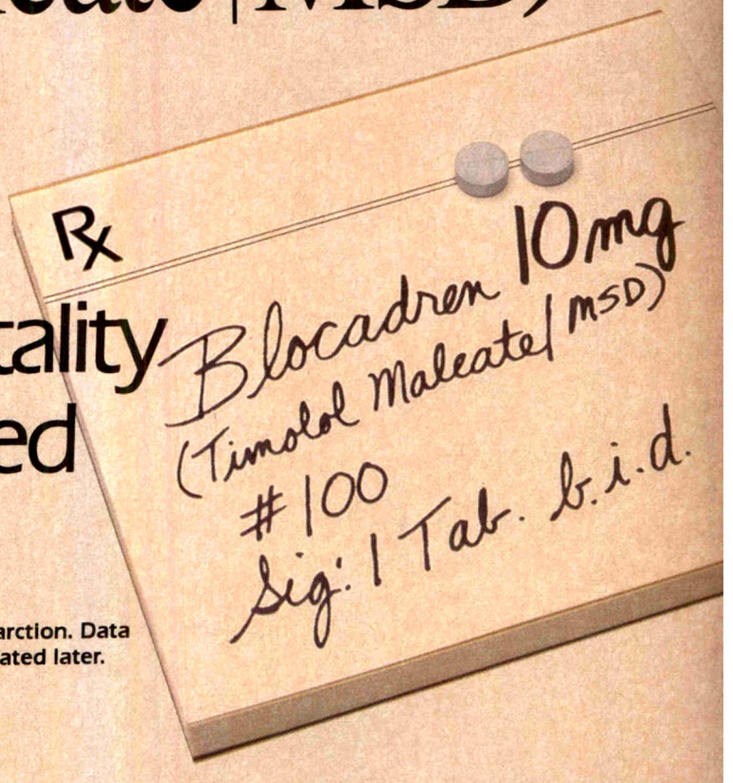
Blocadren®
(Timolol Maleate | MSD)

reduces the risk of reinfarction and cardiac mortality for many stabilized post-MI patients

Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.



disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

BLOCADREN®
(TIMOLOL MALEATE | MSD)

CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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blocked in 5 of 18 patients in a retrograde direction, and in 6 of 17 patients in an anterograde direction. Circus movement tachycardia could be induced in 14 patients before and in 10 patients after the drug. The cycle length of the tachycardia increased from 326 ± 40 to 364 ± 67 ms. In 15 patients atrial fibrillation was induced. In 5 patients anterograde conduction was blocked, in the other patients the shortest R-R interval over the accessory pathway increased from 228 ± 35 to 304 ± 103 ms. Thus, lorcainide excerted a pronounced negative dromotropic effect on the conduction properties of the accessory pathway.

1623 Electrophysiologic Testing in the Management of Patients With the Wolff-Parkinson-White Syndrome and Atrial Fibrillation

FRED MORADY, CARLOS SLEDGE, EDWARD SHEN, RUEY J. SUNG, ROLANDO GONZALES, and MELVIN M. SCHEINMAN

Twenty patients with the Wolff-Parkinson-White syndrome and symptomatic atrial fibrillation underwent electrophysiologic testing. Six patients underwent surgical bypass tract ablation and 14 were treated medically, based on the results of electropharmacologic testing. Over a mean follow-up period of 35 months, only 1 patient treated medically had a recurrence of atrial fibrillation. Successful medical therapy was predicted by the inability to induce atrial fibrillation and atrioventricular reciprocating tachycardia during drug testing or with the induction of atrial fibrillation with a ratio <200 beats/min and a shortest preexcited R-R interval of >250 ms. Electrophysiologic testing can identify patients with Wolff-Parkinson-White syndrome and atrial fibrillation in whom medical therapy is a suitable alternative to bypass tract ablation.

1629 Long-Term Recording of Monophasic Action Potentials From Human Endocardium

MICHAEL R. FRANZ

In this study of 36 patients, a new "contact electrode" catheter technique was used to record monophasic action potentials from atrial and ventricular endocardium without the application of suction. Continuous recordings were of stable amplitude and, at a constant paced frequency, highly reproducible for test periods of 1 hour, permitting direct evaluation of the effect of cycle length alterations on local myocardial repolarization. Duration and configuration of the monophasic action potential were similar to those previously described in intracellular recordings from excised ventricular muscle and showed appropriate changes in response to abrupt and sustained cycle length alterations. Monophasic action potentials could not be recorded from areas of scar, indicating that local viable myocardium is a prerequisite for the generation of the monophasic signal. This technique may provide important information concerning cellular electrical events in man.

CONGESTIVE HEART FAILURE

1635 Association of Hyponatremia With Increased Renin Activity in Chronic Congestive Heart Failure: Impact of Diuretic Therapy

GARY L. SCHAER, ANDREW B. COVIT, JOHN H. LARAGH, and ROBERT J. CODY

The interrelation of serum sodium, prerenal azotemia, and plasma renin activity (PRA) was evaluated in 44 patients with chronic stable heart failure while diuretic therapy was maintained and in 12 similarly ill heart failure patients placed on sodium balance diets (10 and 100 mEq/day) after diuretic therapy was discontinued. The diuretic group showed inverse correlations between serum sodium and PRA ($r = -0.389$, $p < 0.02$) and blood urea nitrogen (BUN)/creatinine ratio ($r = -0.332$, $p < 0.025$). A positive correlation between BUN/creatinine ratio and PRA was noted ($r = 0.365$, $p < 0.025$), with all 3 parameters interrelated by multiple regression analysis ($p < 0.01$). The sodium balance nondiuretic group revealed no statistically significant sodium, BUN/creatinine ratio, or PRA relationship on either balance diet. These results suggest that the prediction of high PRA and angiotensin mediated vasoconstriction, based on the presence of hyponatremia, is highly variable and significantly influenced by diuretic therapy. Although some clinical value may be derived from such associations, the serum sodium-PRA correlation should not be used to draw major inferences regarding the severity of heart failure or the pathophysiology of water balance in patients with heart failure.

1639 Respiratory Gas Analysis During Exercise as a Noninvasive Measure of Lactate Concentration in Chronic Congestive Heart Failure

JOHN R. WILSON, NANCY FERRARO, and KARL T. WEBER

During exercise, bicarbonate buffering of lactate produces carbon dioxide (CO_2) in excess of that resulting from oxidative metabolism. To determine whether calculation of this excess CO_2 production from respiratory gas analysis provides a useful index of blood lactate in patients with heart failure, 22 patients with depressed left ventricular function were studied during progressive maximal upright bicycle exercise. Exercise increased $\dot{V}O_2$, O_2, lactate, and the cardiac index. The increase in lactate at each work load was linearly related to excess production of CO_2 ($r = 0.92$, $p < 0.01$). Exercise was repeated in 10 patients; measurement of excess CO_2 was highly reproducible ($r = 0.98$, $p < 0.01$). Excess CO_2 also correlated with the decrease in bicarbonate produced

Continued on page A26

by exercise (r = 0.81), supporting the hypothesis that excess CO_2 is produced by
tate. Thus, calculation of excess CO_2 provides a reliable and reproducible method
terations in lactate throughout bicycle exercise in patients with chronic heart failu

VALVULAR HEART DISEASE

**1644 Conduction Disturbances Related to the Site and Severity of Mitral Anular Ca
A 2-Dimensional Echocardiographic and Electrocardiographic Correlative St**

TOSHIHIKO TAKAMOTO and RICHARD L. POPP

To investigate an apparent association of mitral anular calcium (MAC) and electro
the relation between location of 2-dimensional (2-D) echo-quantified MAC and
studied in 140 patients with MAC (MAC group) and in 135 age- and sex-matched p
group). The MAC group was subclassified regarding site and severity of calcium in
MAC was defined as Type I, near the primary conduction system—MAC located i
extending to the anterior mitral leaflet; and Type II—MAC located at the central a
from the primary conduction system. The severity of MAC was graded on 2-D ech
ized within 1 segment) and moderate to severe (>1 segment). The data suggest that
of MAC located near the conduction system are associated with conduction distu
tricular conduction delay.

**1650 Analysis of Surgical Versus Medical Therapy in Active Complicated Native Va
Endocarditis**

CHARLES H. CROFT, WAYNE WOODWARD, ALAN ELLIOTT, PATRICK J. CO
N. BARNARD, and WALTER BECK

Comparison of 23 patients with active complicated native valve infective endocardit
ment and 85 patients matched for severity of disease who were managed medicall
rate during the hospital admission is significantly better in those treated surgically. T
gical treatment on hospital mortality largely accounts for differences in long-term su
High-risk subsets of patients treated surgically are those with prolonged preoperativ
those with an aortic root absess. The former are liable to early postoperative recurre
erative prosthetic paravalvular regurgitation. Aortic valve involvement carries an unf
sis compared with mitral valve involvement in patients treated medically, and this adv
ably improved in surgically managed patients. These results indicate that surgery sh
the management of patients with complicated active infective endocarditis.

1656 BOOKS RECEIVED

MISCELLANEOUS TOPICS

1657 Coronary Dilatory Capacity in Idiopathic Dilated Cardiomyopathy: Analysis of 1

DIETER OPHERK, FRANZ SCHWARZ, GERHARD MALL, JOACHIM MANTHEY, D
WOLFGANG KÜBLER

Patients with idiopathic dilated cardiomyopathy frequently have chest pain suggesti
despite the presence of widely patent coronary arteries. Therefore, in 16 patients wi
myopathy, coronary blood flow was measured at rest and after intravenous applicati
to determine coronary dilatory capacity. In patients with idiopathic dilated cardiomyo
reserve was markedly reduced ($p < 0.001$ compared with control values). There w
tween minimal coronary resistance and left ventricular end-diastolic pressure (r = 0.
ular catheter biopsy specimens revealed no alterations in myocardial microvasculat
duction of coronary dilatory capacity in patients with idiopathic dilated cardiomyopath
by an increase in extravascular intramyocardial pressure resulting in increased coro

**1663 Prevalence and Significance of an Abnormal S-T Segment Response to Exercis
Population**

PAOLO SPIRITO, BARRY J. MARON, ROBERT O. BONOW, and STEPHEN E. E

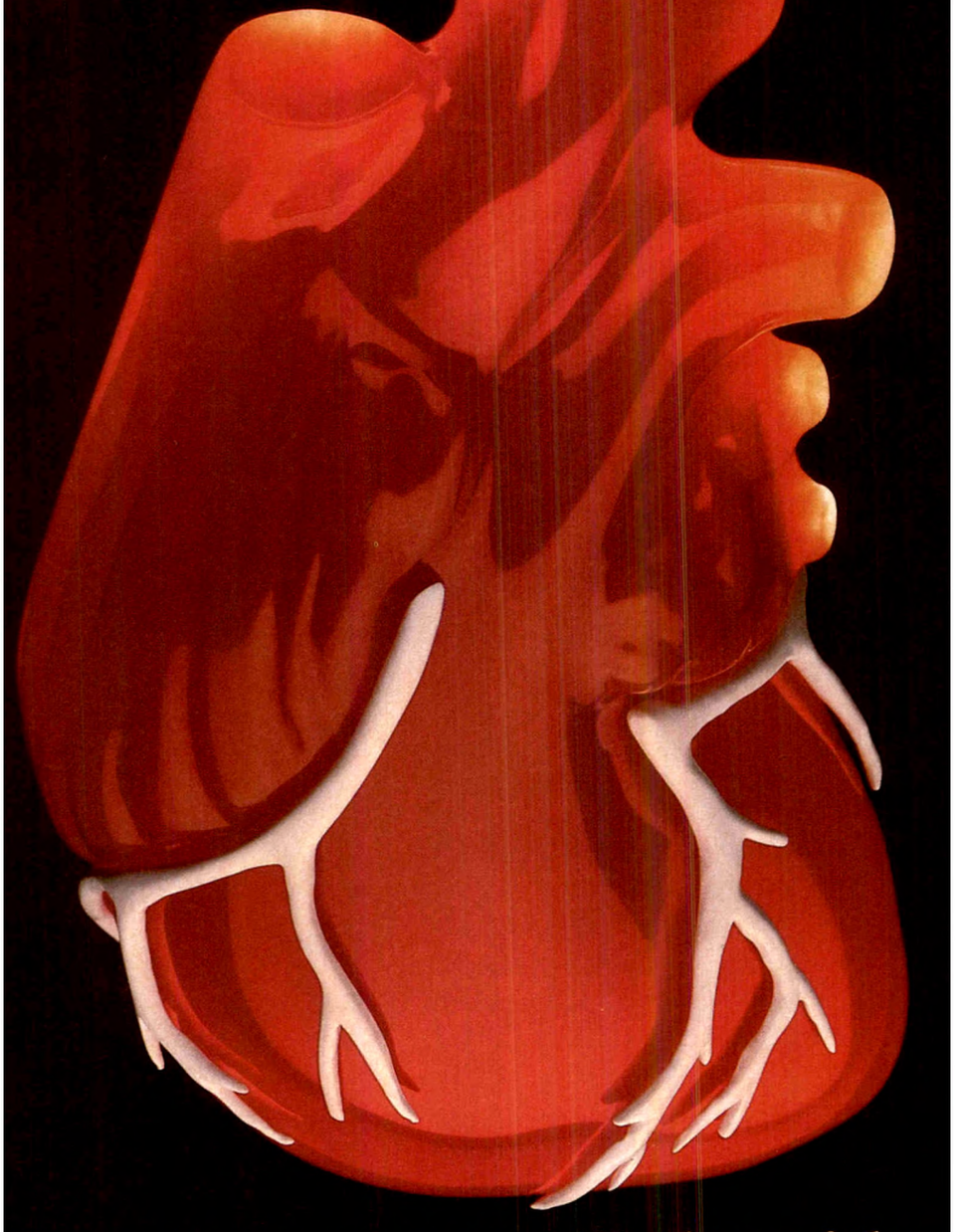
To determine the frequency and significance of an abnormal S-T segment response
letes with increased left ventricular (LV) mass induced by physical conditioning, 75
athletes without evidence of heart disease (mean age 21 years) and 48 nonathletic yo

Continued on page A34

Announcing a major advance
in cardiovascular therapy

New CARDIZEM™ (diltiazem HCl)

CALCIUM CHANNEL BLOCKADE
from Marion Laboratories



Potent coronary vasodilation with a distinctive hemodynamic profile

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cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY WITH A LOW INCIDENCE OF SIDE EFFECTS

CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

These changes provide effective therapy with a low incidence of side effects.

Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

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CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries.[1]

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

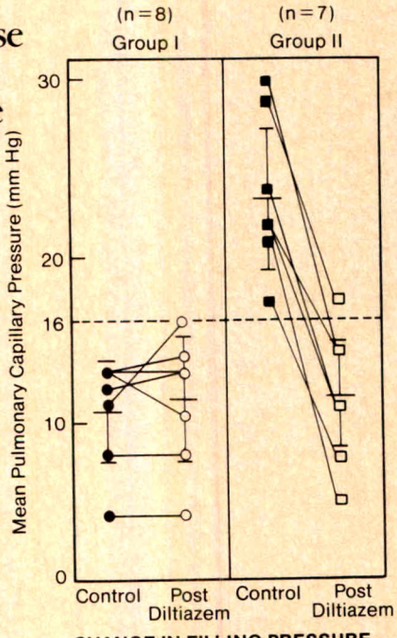
While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.



CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

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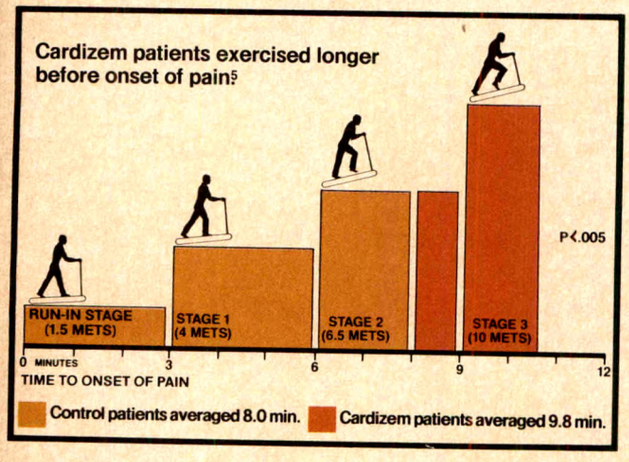
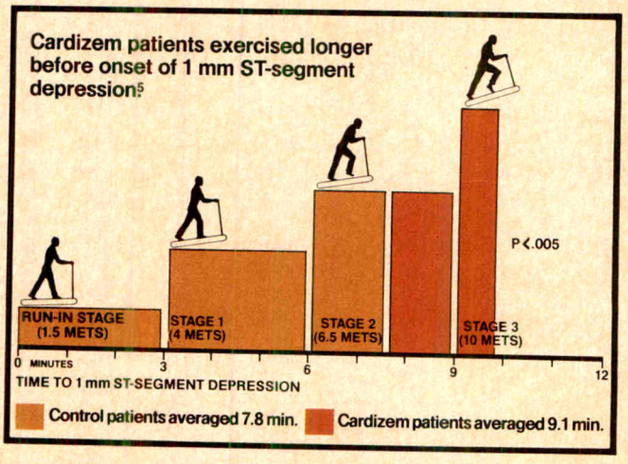
1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.

Please see full prescribing information on last page of this ad.

EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:

A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

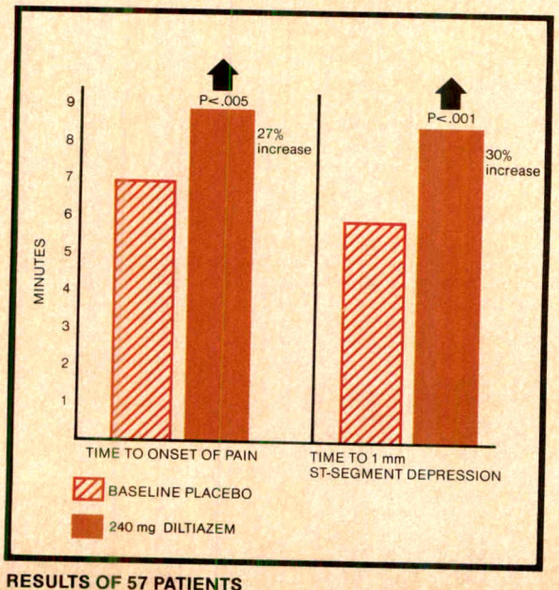
5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.

6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

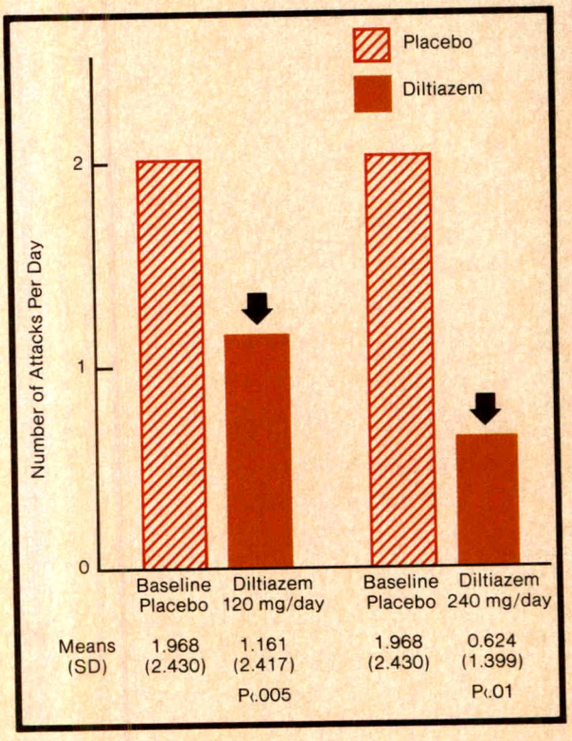
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



7. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

Please see full prescribing information on last page of this ad.

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

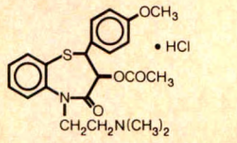
PROFESSIONAL INFORMATION

cardizem™ (diltiazem HCl)

30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in controlling anginal symptoms, including documented ECG changes, in patients presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

1/83

studied by M-mode echocardiography and exercise electrocardiography. Ventricular septal and posterior free wall thicknesses and calculated LV mass were significantly greater in athletes than in control subjects. An abnormal S-T segment response to exercise was present in 7 (9%) of the 75 athletes, all of whom had LV mass >275 g, and in 5 the LV mass was above the 95th percentile of that of the control subjects. An abnormal treadmill exercise test also was present in 3 (6%) of 48 controls. Abnormal results on exercise tests occur commonly in both athletes and nonathletes. The fact that almost 10% of isometrically trained athletes have "false-positive" exercise electrocardiograms suggests that this test has major limitations in screening athletes for underlying cardiovascular disease.

1667 Heterogeneity of Left Ventricular Segmental Wall Thickening and Excursion in 2-Dimensional Echocardiograms of Normal Human Subjects

NATESA G. PANDIAN, DAVID J. SKORTON, STEVE M. COLLINS, HERMAN L. FALSETTI, EDMUND R. BURKE, and RICHARD E. KERBER

Two-dimensional (2-D) echocardiograms from 12 normal men were analyzed to determine the normal range of segmental left ventricular (LV) contraction using echocardiography. Short-axis images at mitral valve, chordal, papillary muscle, and apical levels were obtained at end-diastole and end-systole, and each image was divided by computer into 12 cavity and wall segments. The overall range of cavity segment area change was 0 to 100%, and of segmental wall thickening 0 to 150%. Significant differences were found between adjacent segments and between subjects. We conclude that considerable intersegmental and intersubject variability of left ventricular contraction occurs in normals as exhibited on 2-D echocardiograms. Because significant differences in segmental wall thickening and endocardial excursion may be exhibited in echos of normal subjects, such differences alone may not indicate cardiac disease.

1674 Cardiac Function in Sickle Cell Anemia

BARRY S. DENENBERG, GERARD CRINER, RICHARD JONES, and JAMES F. SPANN

Although ventricular dysfunction is suspected to underlie congestive heart failure in sickle cell anemia (SCA), ejection indexes of left ventricular (LV) pump function are normal. Increased preload and decreased afterload of SCA increase the ejection indexes and might obscure LV dysfunction. Therefore, the preload and afterload independent stress-volume index was compared in 11 patients with SCA and 11 normal subjects. Systemic vascular resistance (afterload) was decreased in SCA. End-diastolic volume index (preload) was increased in SCA. Ejection fractions were similar in the 2 groups. In patients with SCA, the resting end-systolic stress-volume index was decreased and the slope of the end-systolic stress versus end-systolic volume index relation was also decreased, suggesting LV dysfunction in those patients. Thus, the intrinsic muscle contractile performance is depressed in SCA. Increased preload and decreased afterload compensate for LV dysfunction and maintain a normal ejection fraction and high cardiac output.

1679 Cardiac Disease After Radiation Therapy for Hodgkin's Disease: Analysis of 48 Patients

MARK M. APPLEFELD and PETER H. WIERNIK

Delayed cardiac disease as a consequence of previous thoracic radiation therapy for Hodgkin's disease may be more common than previously believed. This hypothesis was tested by performing detailed cardiac evaluations in 48 patients 37 to 172 (mean 97) months after radiotherapy. Evaluation identified cardiac disease in 46 of 48 (96%) of these patients. The disorders most often identified were chronic pericarditis (24 patients), an abnormal hemodynamic response to fluid challenge (14 patients), and coronary artery disease (6 patients). Excluding patients with coronary artery disease, left ventricular systolic function as assessed by gated radionuclide ventriculography was normal at rest and during exercise. Six patients underwent pericardiectomy for constrictive pericarditis: 3 had a good operative result; 2 have persistent symptoms postoperatively, presumably caused by visceral pericardial constriction; and a third patient died from progressive Hodgkin's disease. Three other patients had coronary artery bypass surgery for occlusive coronary artery disease. Surgery was successful in 2 patients; 1 patient died after operation at another center. Two patients have congestive heart failure and are moderately disabled. The remaining 35 patients are not significantly limited by their cardiac symptoms. Thus, although delayed cardiac disease after radiotherapy may be common, its prognosis appears excellent.

1682 Contrasting Acute Effects of Vasodilators (Nitroglycerin, Nitroprusside, and Hydralazine) on Right Ventricular Performance in Patients With Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension: A Combined Radionuclide-Hemodynamic Study

BRUCE N. BRENT, HARVEY J. BERGER, RICHARD A. MATTHAY, DONALD MAHLER, LINDA PYTLIK, and BARRY L. ZARET

A combined radionuclide-hemodynamic approach was used to assess the effects of nitroglycerin, nitroprusside, and hydralazine on right ventricular performance and central hemodynamics in patients with chronic obstructive pulmonary disease. Nitroglycerin and nitroprusside significantly decreased mean right atrial pressure, right ven-

Continued on page A43

New and important evidence affirms the

Slow-K®

potassium chloride slow-release tablets 8 mEq

8-year U.S. record of clinical experience.

Please see last page for brief Prescribing Information.

New endoscopic studies show:

No significant difference in GI lesions between

Slow-K®
potassium chloride
slow-release tablets 8 mEq

and
Micro-K®
potassium chloride
controlled-release Extencaps®
600 mg 8 mEq K

SLOW-K: UNSURPASSED FOR SAFETY AMONG SLOW-RELEASE KCl CAPSULES OR TABLETS

Maximum-dosage (96 mEq) multistudy data*

Results: No significant differences in endoscopic changes found between Slow-K and Micro-K at 96-mEq dosage.†

(Administered as four 8-mEq tablets or capsules, t.i.d.)

These data resulted from four different studies (involving 64 subjects) that used the maximum recommended daily dosage of 96 mEq before food ingestion and with concomitant administration of the maximum recommended dosage of the anticholinergic agent glycopyrrolate (6 mg).[1-4]

Maximum-dosage multistudy data

					Endoscopic findings‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
27	Slow-K	96 mEq	6 mg	No	1	1	6	12
37	Micro-K	96 mEq	6 mg	No	2	1	2	9

Results from similar studies supported by the A.H. Robins Company have shown a greater incidence of endoscopically observed GI irritation with Slow-K as compared to Micro-K when maximum doses of glycopyrrolate are administered.[5,6] These results, showing a significant difference between the products, are *inconsistent* with the data described herein, which do not show a significant difference.

High-dosage (48 mEq) multistudy data*

Results: No ulcers found with Slow-K or Micro-K. No significant differences in endoscopic changes found with Slow-K and Micro-K at 48-mEq dosage.

(Administered as two 8-mEq tablets or capsules, t.i.d.)

These data resulted from four different studies (involving 36 subjects) that used the high (48 mEq) dosage with food ingestion, and with and without the maximum recommended dosage of the anticholinergic agent glycopyrrolate. (Note: Glycopyrrolate was used in only one group of subjects on Slow-K.)[1-4] This 48-mEq dosage is higher than that normally used prophylactically.

High-dosage multistudy data

					Endoscopic findings‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
12	Slow-K	48 mEq	6 mg	Yes	0	0	2	6
12	Slow-K	48 mEq	None	Yes	0	0	0	4
12	Micro-K	48 mEq	None	Yes	0	0	1	5

*These studies were conducted by Drs. D. Patterson and G. Jeffries of the Hershey Medical Center, and by Dr. D. Earnest of the University of Arizona (Tucson).

†Also included in these multistudy data were an additional 70 subjects taking an 8-mEq sustained-release KCl capsule, a K^+ elixir, a sustained-release KCl tablet of higher mEq dosage than that currently available, or a placebo. The elixir and the placebo did not produce any endoscopic changes greater than two Grade 1 and five Grade 1 endoscopic findings, respectively. The higher dose sustained-release KCl tablets produced two ulcers, two Grade 2 and six Grade 1 endoscopic findings. The 8-mEq sustained-release capsule produced two Grade 2 and two Grade 1 findings. All Grade 1 endoscopic changes were considered clinically meaningless.

‡Grade 0 = no endoscopic findings
1 = hyperemia and/or edema (the medical consensus is that this category is clinically meaningless)
2 = few erosions
3 = numerous erosions (>3)
4 = ulceration
5 = multiple ulcerations

The anticholinergic agent glycopyrrolate was given to slow gastric emptying, thus ensuring maximum contact of the KCl supplements with the gastric mucosa. The impact, if any, of high-dose glycopyrrolate on the gastric mucosa is unknown.

Please see last page for brief Prescribing Information.

CIBA

New epidemiologic study shows:

No difference between

Slow-K®

potassium chloride slow-release tablets 8 mEq

use and no K^+ therapy in the incidence of upper GI bleeding in a hospital setting.

SLOW-K: UNSURPASSED FOR SAFETY AMONG SLOW-RELEASE KCl CAPSULES OR TABLETS

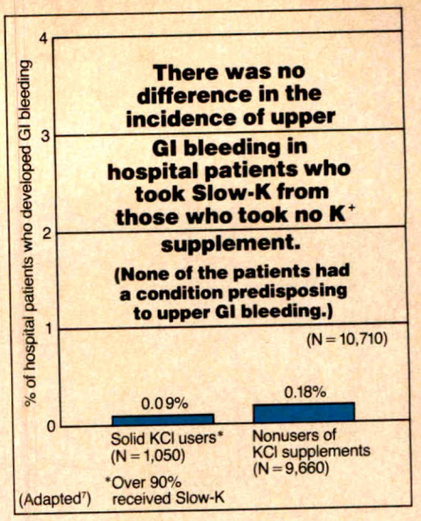
Experience of the Boston Collaborative Drug Surveillance Program[7]
As reported by Aselton and Jick in *Lancet,* January 22, 1983

Purpose of epidemiologic study:
To evaluate the relation between the use of wax-matrix KCl and the development of upper GI bleeding while in the hospital.

Patient population:
A total of 15,791 medical inpatients. Of those, 10,710 had no condition predisposing to upper GI bleeding. Of those, 1,050 received solid KCl* by mouth; 9,660 received no solid KCl.

Findings:
Of the 1,050 KCl users, 1 had GI bleeding (0.09%).
Of the 9,660 nonusers, 17 had GI bleeding (0.18%).

*Over 90% of this group received KCl in the form of Slow-K tablets.



Conclusion: "These findings argue against a positive association between wax matrix KCl use and upper gastrointestinal bleeding over a short period of time."[7]

These new data are consistent with the overwhelming evidence compiled in 8 years of use with Slow-K® potassium chloride slow-release tablets 8 mEq.

Analysis of 5.6 million U.S. patient-years' data: approximately one GI lesion per 100,000 patient-years--and this incidence rate has remained unchanged since Slow-K was introduced in 1975.[8]

*Method of determining incidence:
A: Includes all cases (most conservative method)
B: Excludes cases in which causality was unlikely and/or Slow-K was contraindicated
C: Excludes cases in which B was present *and* in which data were insufficient to assess causality (least conservative method)

Summary of lesion incidence rates per 100,000 patient-years

	Method* A	B	C
Esophagus	0.14	0.02	0.02
Stomach	0.27	0.14	0.11
Duodenum	0.12	0.05	0.05
Small bowel/large bowel; unknown location	0.82	0.43	0.27
Total	1.36	0.64	0.44

(Adapted[8])

Conclusion: Slow-K is a safe agent.

Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Please see last page for brief Prescribing Information.

CIBA

Slow-K®

potassium chloride slow-release tablets 8 mEq

Unsurpassed among K^+ capsules or tablets for clinical safety*

Unrivaled among K^+ capsules or tablets for clinical experience

* Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

- 7.3 million patients treated through 1981
- Over 2 million additional patients in 1982 alone
- Over 51.8 million new and refill prescriptions
- 8 years' U.S. clinical experience
- 17 years' worldwide clinical experience
- 5.6 million U.S. patient-years of use
- Listed on 80-85% of the larger U.S. hospital formularies

(Data on file, CIBA Pharmaceutical Company.)

Do you have any questions concerning Slow-K? A member of the CIBA medical staff would be happy to answer them.

Please write to:
Dr. Richard H. Roberts
Director of Professional Affairs
CIBA Pharmaceutical Company
556 Morris Avenue
Summit, New Jersey 07901

References

1. Patterson D, Jeffries G: Endoscopic comparison of Slow-K tablets and Micro-K capsules in 30 subjects as reported to the Cardiovascular and Renal Drugs and Gastrointestinal Drugs Advisory Committees, March 2, 1983. Data on file, CIBA Pharmaceutical Company.
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8. Data on file, CIBA Pharmaceutical Company.

Please turn page for brief Prescribing Information.

CIBA

SLOW-K®
potassium chloride slow-release tablets

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distension, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 40 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

Consult complete product information before prescribing.

CIBA Pharmaceutical Company
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Summit, New Jersey 07901

128-6245-A

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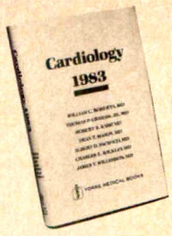
Cardiology 1983



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tricular end-diastolic volume index, mean pulmonary artery pressure, cardiac index, and arterial oxygen tension. Nitroglycerin did not affect pulmonary vascular resistance but increased right ventricular ejection fraction. Nitroprusside mildly decreased pulmonary vascular resistance but did not alter right ventricular ejection fraction. In contrast, hydralazine decreased pulmonary vascular resistance and increased cardiac index and right ventricular ejection fraction. The increase in ejection fraction correlated well with the decrease in pulmonary vascular resistance. These data suggest that in patients with mild to moderate secondary pulmonary hypertension, acute administration of hydralazine results in substantial improvement of right ventricular performance by virtue of decreasing pulmonary vascular resistance. In contrast, nitroglycerin and nitroprusside demonstrate predominant effects that reduce preload, cardiac index, and arterial oxygen tension.

CONGENITAL HEART DISEASE

1690 Reoperation for Isthmic Coarctation of the Aorta: Follow-Up of 26 Patients

PHYLLIS POLLACK, MICHAEL D. FREED, ALDO R. CASTANEDA, and WILLIAM I. NORWOOD

Although repair of coarctation of the aorta is a common and safe procedure, inadequate relief or restenosis requiring reoperation is not unusual. The results of reoperation for coarctation of the aorta rarely have been evaluated. This series presents follow-up results in 26 patients who underwent reoperation for coarctation of the aorta. There was no morbidity or mortality. Resting coarctation pressure gradients and arm systolic blood pressures were significantly improved. Systolic hypertension persisted in 5 of 25 patients (20%) on follow-up. Patch aortoplasty appears to be a safe and satisfactory surgical approach. Reoperation for coarctation of the aorta is a very low-risk procedure that improves symptoms and relieves residual or recurrent obstruction. Systolic hypertension, however, does not always resolve postoperatively.

1695 Subxyphoid 2-Dimensional Echocardiographic Identification of Left Ventricular Papillary Muscle Anomalies in Complete Common Atrioventricular Canal

ALVIN J. CHIN, FREDRICK BIERMAN, STEPHEN P. SANDERS, ROBERTA G. WILLIAMS, WILLIAM I. NORWOOD, and ALDO R. CASTANEDA

Two-dimensional (2-D) echocardiography was performed in 31 infants with complete common atrioventricular (AV) canal. Eighty percent had 2 left ventricular (LV) papillary muscles on 2-D echocardiography, 10% had 3 LV papillary muscles, and 10% had a solitary LV papillary muscle. Among the 25 infants with complete common AV canal with 2 LV papillary muscles, there was 1 operative death. Among the 6 infants with complete common AV canal with LV papillary muscle anomalies, 5 underwent surgical repair with 4 early deaths. Subxyphoid 2-D echocardiography is a useful technique for evaluating LV papillary muscle architecture in patients with complete common AV canal and permits identification of those who may be at higher risk for unsuccessful mitral reconstruction.

1701 Anatomic Obstruction of the Right Ventricular Outflow Tract in Transposition of the Great Arteries

RUDOLF J. MOENE, ARENTJE OPPENHEIMER-DEKKER, and MARGOT M. BARTELINGS

In 126 postmortem specimens with transposition of the great arteries (combined with a ventricular septal defect in 55 cases), the morphologic features of the right ventricular outflow tract were studied with the aim of tracing possible relationships with potential subaortic obstruction. Distinct anatomic obstruction was found in 15 hearts with and 2 hearts without ventricular septal defect. The obstruction resulted from anterior displacement of infundibular septum and ventriculoinfundibular fold (12 cases), from bulging of the trabecula septomarginalis and/or ventriculoinfundibular fold (3 cases), or from aberrant muscle bundles (2 cases). Associated anomalies indicative of prenatal subaortic obstruction were dimensional aortic arch malformations in 6 specimens. Six cases had tricuspid valve anomalies. It is concluded that subaortic obstruction may constitute a complicating factor in transposition of the great arteries; it is suggested that in these cases a "switch" procedure might prevent progression of obstruction resulting from maintained systemic blood pressure in the right ventricle.

1705 Quantitative Angiographic and Morphologic Aspects of Aortic Valve Atresia

ALOIS R. HASTREITER, RONALD L. VAN DER HORST, IRA W. DUBROW, and FRIEDRICH O. ECKNER

Quantitative angiographic measurements were performed on 15 infants aged 1 to 35 days who had aortic valve atresia with intact ventricular septum and hypoplastic left ventricle. Thirteen of these infants had similar measurements performed at autopsy. The latter measurements were smaller than those found at angiography (because of shrinkage), but their relationship was predictable. Angiographic right ventricular (RV) volumes were 2 and 4 times normal in diastole and systole, respectively. The RV volume measured at autopsy was >3 times normal. Mean RV ejection fraction was 0.40; it was below normal in 10 infants. Maximal right atrial volume was >2 times normal, and the mean left atrial maximal volume was two-thirds normal. The relation between circumferences of the aortic arch and the ascending and descending aorta was similar at angiography and autopsy.

Continued on page A47

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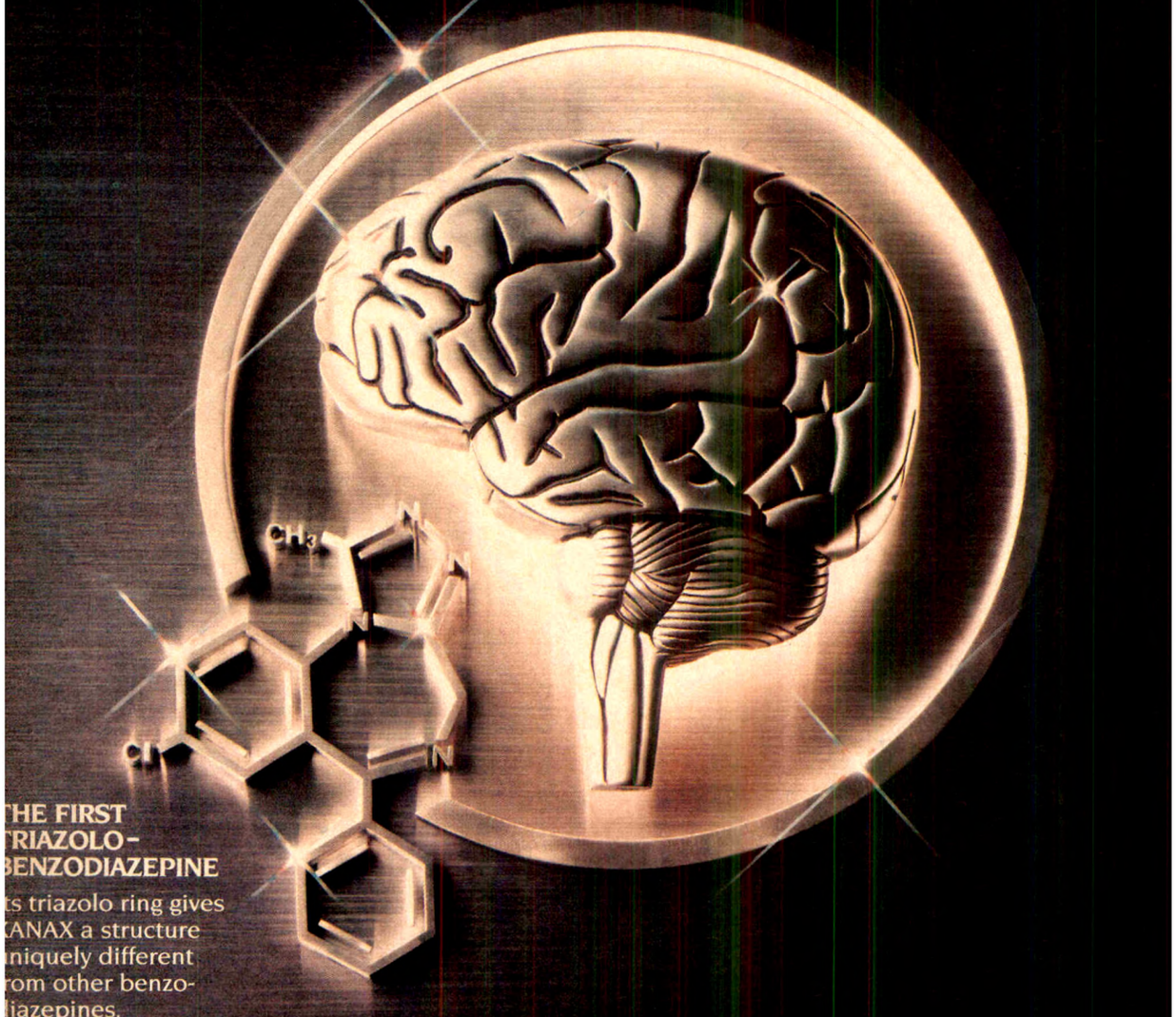

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FOR CLINICAL ANXIETY

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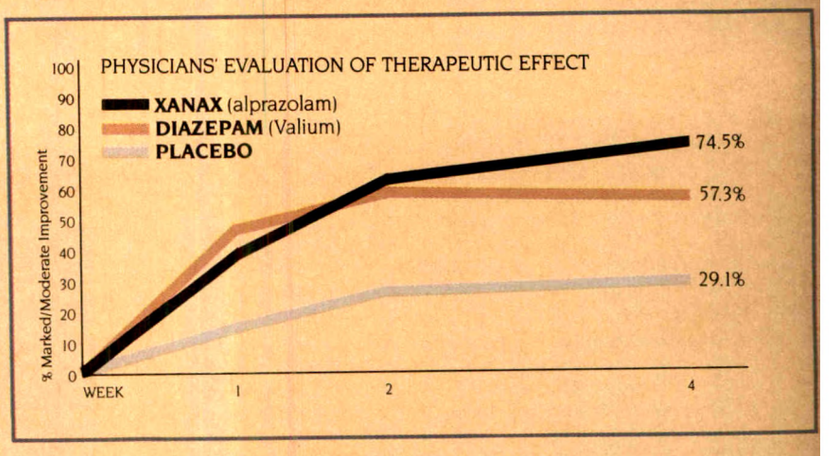
In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam (Valium).*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy (Valium) in *a 976-patient*, placebo-controlled, multicenter study.*

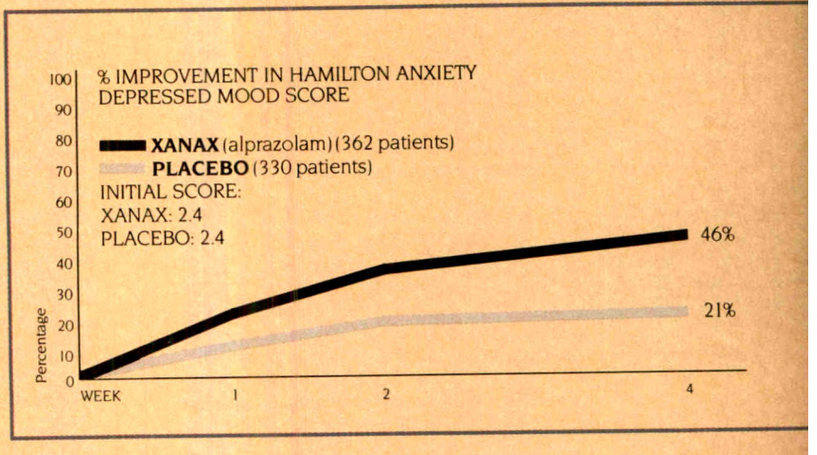


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

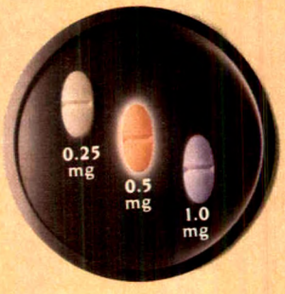
EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE:
XANAX 0.25–0.5 mg T.I.D.



The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

Xanax® 0.5 mg Tablets
alprazolam C-IV

XANAX® Tablets ©
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 42 (9):347-351, 1981.

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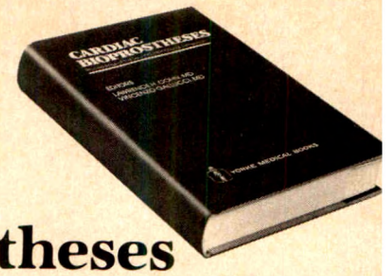

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MI
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology,* now available in its second issue, *Cardiology 1982.*

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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METHODS

1709 Increased Left Ventricular Ejection Fraction After a Meal: Potential Source of Error in Performance of Radionuclide Angiography

JERRY M. BROWN, CHRISTOPHER J. WHITE, SAMUEL M. SOBOL, and ROBERT J. LULL

To study the effects of eating on cardiac performance in man, the left ventricular ejection fraction was determined by radionuclide angiography before and after a standardized meal in 16 patients with compensated congestive heart failure. Patients with moderate depression of fasting left ventricular ejection fraction (30 to 50%) had significant increases in left ventricular ejection fraction after a meal. Patients with a severely depressed fasting left ventricular ejection fraction (<30%) had no increase after a meal. Thus, patients' mealtimes constitute an important unmeasured variable in the determination of left ventricular ejection fraction in patients with moderate but not severe left ventricular dysfunction.

1712 Diagnostic Accuracy of Indium-111 Platelet Scintigraphy in Identifying Left Ventricular Thrombi

MICHAEL D. EZEKOWITZ, ROBERT D. BURROW, PAUL W. HEATH, TERRI STREITZ, EILEEN O. SMITH, and DONALD E. PARKER

A retrospective, blinded analysis is presented of 662 indium-111 platelet images from 64 patients read on 2 separate occasions by 3 observers. Tissue confirmation of the presence or absence of thrombus was made at surgery or autopsy. Results indicate that a comparison of images obtained in the left anterior oblique view on the day of injection with those obtained 3 to 4 days later provides the best combination for determining sensitivity, diagnostic accuracy, and specificity (65, 99, and 99%, respectively). Imaging in multiple views (right anterior oblique, anterior, left anterior oblique, and left lateral) greatly facilitates localization of thrombus to the left ventricle. This study also defines the reproducibility of this technique, the mean intraobserver and interobserver agreement being 91 and 88%, respectively.

EXPERIMENTAL STUDIES

1717 Tissue Digoxin Concentrations During the Quinidine-Digoxin Interaction

NATALIE J. WARNER, EDWARD B. LEAHEY, Jr., THOMAS J. HOUGEN, J. THOMAS BIGGER, Jr., and THOMAS W. SMITH

Tissue digoxin concentrations were measured in dogs treated with tritiated digoxin and quinidine. After 24 hours of intravenous quinidine, changes in the ratio of tissue-to-serum digoxin concentration ratios found. Renal-to-serum digoxin concentration decreased, and this decrease was proportional to the serum quinidine concentration. Myocardial-to-serum digoxin concentration increased and occipital muscle and medullary brainstem-to-serum digoxin concentration ratios decreased, but these changes were independent of the serum quinidine concentration. After drug doses calculated to result in steady-state serum drug concentrations, no changes in digoxin concentration in myocardium, skeletal muscle, kidney, liver, or brain tissue were found, nor were there changes in the tissue-to-serum digoxin concentration ratio.

1722 Effect of Atrial Fibrillation on Atrial Blood Flow in Conscious Dogs

PHILIP A. McHALE, JUDITH C. REMBERT, and JOSEPH C. GREENFIELD, Jr.

This study examined the independent effects of atrial tachycardia, ventricular tachycardia, and atrial fibrillation (AF) on atrial and ventricular blood flow in conscious, heart-blocked dogs using radioactive microspheres. Atrial blood flow averaged 0.54 ± 0.08 ml/min/g during the control period at an atrial rate of 124 beats/min and a ventricular rate of 90 beats/min. Atrial flow increased to 0.72 ± 0.12 ml/min/g during atrial pacing at 236 beats/min, but was not significantly altered by ventricular pacing at 200 beats/min. AF at a ventricular rate of 90 beats/min resulted in atrial flow values of 0.91 ± 0.08 ml/min/g. Administration of adenosine during AF further increased atrial flow to 2.18 ± 0.16 ml/min/g. Atrial tachycardia or AF did not significantly affect ventricular blood flow. These data indicate (1) that atrial blood flow increases significantly during AF, reaching flow values per gram of tissue comparable to those of the left ventricle, and (2) that this flow is regulated by the metabolic needs of the atrial tissue and does not represent maximal vasodilation.

1728 Relation of Left Ventricular Mass to Geometry of the Proximal Coronary Arteries in the Dog

RICHARD S. STACK, JUDITH C. REMBERT, BRUCE SCHIRMER, and JOSEPH C. GREENFIELD, Jr.

Proximal epicardial coronary artery luminal diameters were measured from silicone casts formed in situ in freshly excised hearts. Twenty-five coronary arteries from 15 normal dogs and 22 coronary arteries in 13 dogs with either chronic pressure or volume overload hypertrophy were studied. A poor correlation existed between left ventricular mass and coronary artery diameter in both normal and hypertrophy groups. The mean cross-sectional area of the combined left circumflex and left anterior descending was 0.12 cm^2 in the normal group and 0.15

Continued on page A48

cm^2 in the hypertrophy group; this increase was not statistically significant ($p = 0.13$). When the mean cross-sectional area of the combined vessels was adjusted for heart weight, there was a decrease in the cross-sectional area per 100 g of myocardium in the hypertrophy group compared with the control group. These data demonstrate that coronary artery luminal diameter does not increase commensurately with the increase in mass associated with myocardial hypertrophy.

1732 Quantitative Detection of Regional Left Ventricular Contraction Abnormalities by 2-Dimensional Echocardiography. Comparison of Myocardial Thickening and Thinning and Endocardial Motion in a Canine Model

JOSEPH E. O'BOYLE, ALFRED F. PARISI, MARKKU NIEMINEN, ROBERT A. KLONER, and SHUKRI KHURI

Two-dimensional echocardiographic studies were analyzed by 2 algorithms for left ventricular contraction abnormalities in 27 dogs after coronary arterial ligation. Both algorithms detected >90% of the myocardial dysfunction associated with myocardial infarction; however, the thickening algorithm identified normal zones better than the cavity area shrinkage algorithm. Neither algorithm had an advantage in predicting the circumferential extent of myocardial infarction. Therefore, either algorithm can be used to detect the presence and quantify the extent of myocardial infarction.

1739 Pharmacologically Induced Changes in Wall Thickening Dynamics and Mid-Ventricular Volumes in Dogs Assessed by Prospectively Gated Computed Tomography

G. B. JOHN MANCINI, WALLACE W. PECK, ROBERT A. SLUTSKY, ROBERT F. MATTREY, and CHARLES B. HIGGINS, *With the technical assistance of* STEPHEN A. LONG

Assessment of regional wall thickening dynamics is important for monitoring the response of normal and ischemic myocardium to pharmacologic interventions. Since regional wall thickness can be measured on computed tomographic scans of the heart, the ability of electrocardiogram-gated computed tomography to determine the effects of pharmacologic agents on global and segmental left ventricular (LV) function was assessed in 8 conditioned dogs. Changes in contractility and loading conditions were produced by infusions by isoproterenol, phenylephrine, and verapamil. An analysis was made of septal, apical and lateral wall thickness, percent wall thickening, end-diastolic and end-systolic mid-LV volume, and percent change in mid-LV volume. Phenylephrine induced significant thinning of the walls and impairment of systolic thickening, whereas isoproterenol induced opposite effects. Despite a lowering of afterload caused by verapamil, wall thickening showed either no change or a deterioration and global function was not improved, signifying a depression of the contractile state. It is concluded that electrocardiogram-gated computed tomography can be used to assess the effects of pharmacologic interventions on global and segmental LV function.

1744 Coronary Blood Flow During the Development and Regression of Left Ventricular Hypertrophy in Renovascular Hypertensive Rats

PIERRE WICKER, ROBERT C. TARAZI, and KIMINARI KOBAYASHI

Left ventricular (LV) coronary flow (CF) was determined by left atrial injection of microspheres in conscious rats during the development and after the reversal of LV hypertrophy in 2-kidney, 1-clip Goldblatt hypertension. Two groups of untreated renal hypertensive rats (RHR) were studied, the first (RHR_1, $n = 17$) at 10 weeks and the second (RHR_2, $n = 9$) at 24 weeks after clipping. Beginning 9 weeks after clipping, 2 other groups were treated either with captopril (40 to 60 mg/kg/day) in drinking water (RHR-C, $n = 8$) or left nephrectomy (RHR-N, $n = 9$) and followed for 15 weeks. Sham-operated animals followed for similar periods of time served as controls (Sham-1, $n = 12$, as a control for RHR_1, and Sham-2, $n = 11$, as a control for RHR_2). In all groups, LV mass increased or decreased in close correlation with changes in arterial blood pressure, and minimal total LV coronary resistance remained unchanged. The development of hypertrophy was associated with a tendency toward reduction in CF reserve (defined as maximal CF/unit mass); this flow reserve was restored with reversal of hypertrophy. The importance of the relation between pressure and LV mass as a determinant of CF reserve was investigated in a second study in which this relation was changed by altering the periods of captopril therapy; in these cases, CF reserve correlated significantly with the ratio of arterial pressure to LV mass ($r = 0.76$, $n = 12$, $p < 0.01$). The results suggest that maintenance of CF reserve in LV hypertrophy depends on an appropriate balance between arterial pressure and LV mass, and might be disturbed by antihypertensive therapy that leaves LV hypertrophy unchanged.

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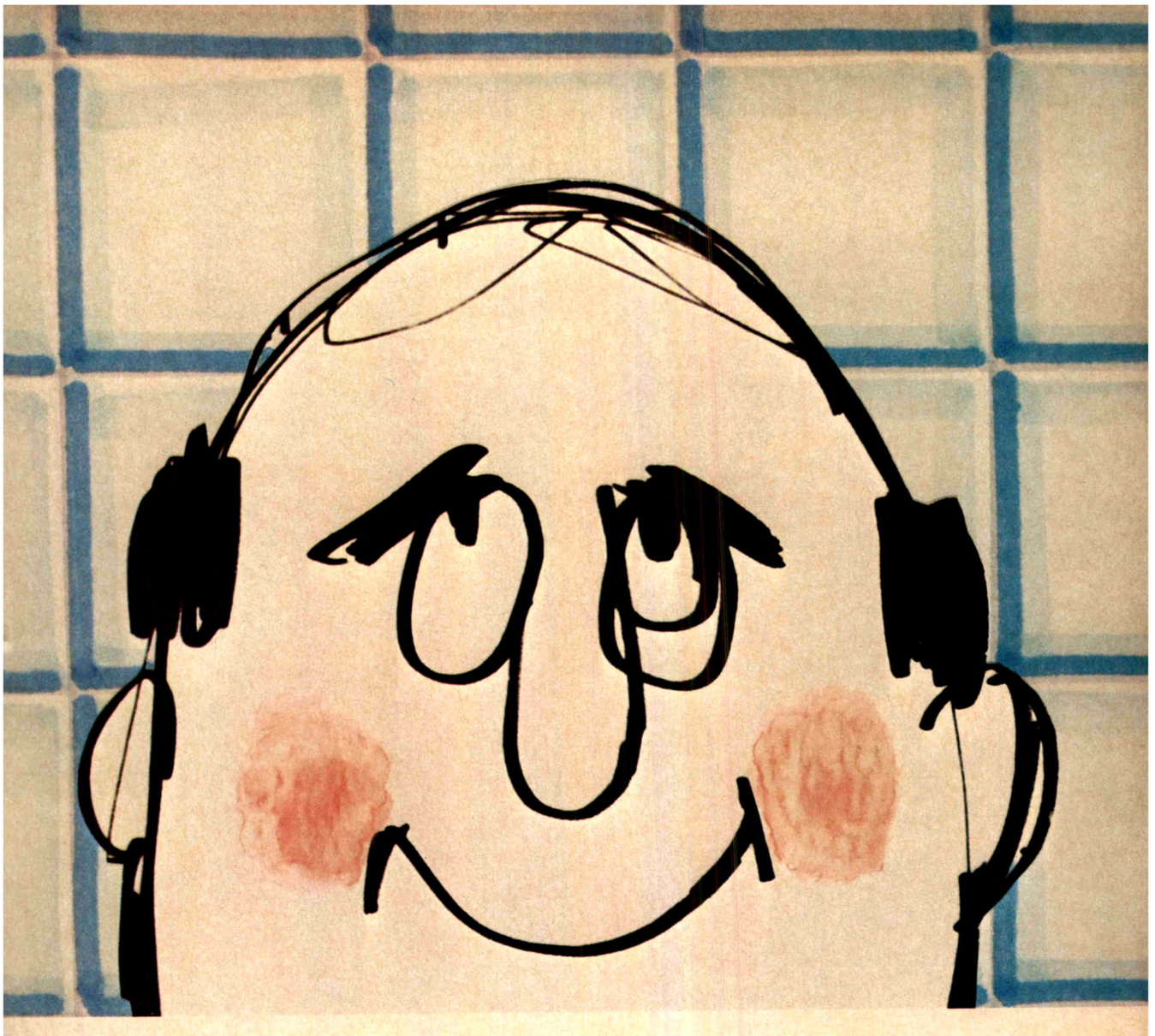

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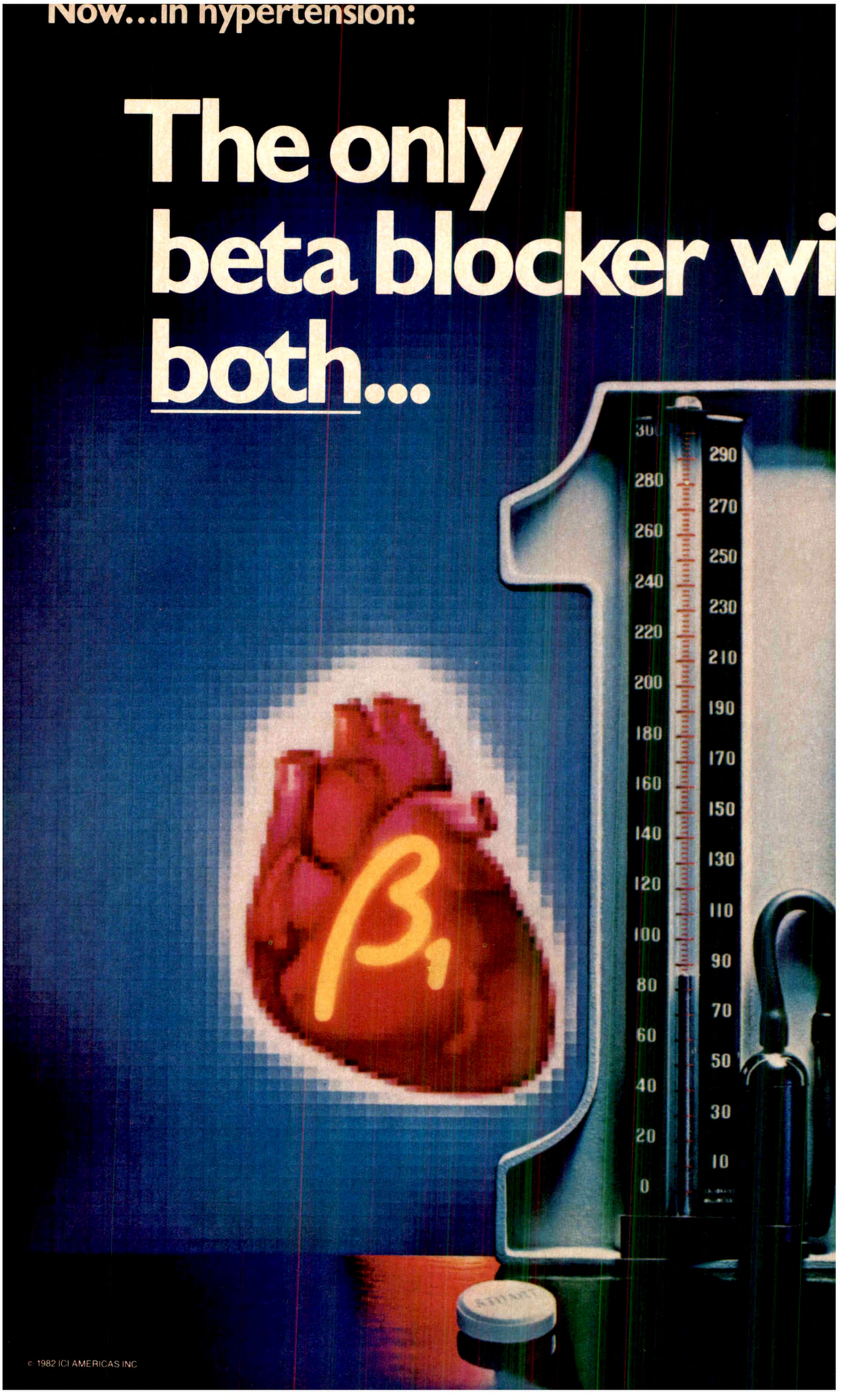
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See last page of this advertisement for brief summary of prescribing information

TENORMIN® (atenolol)

A beta$_1$-selective blocking agent for hypertension.

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

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1750 End-Systolic Dimension-Wall Thickness Relations During Myocardial Ischemia in Conscious Dogs. A New Approach for Defining Regional Function

GENTA OSAKADA, OTTO M. HESS, KIM P. GALLAGHER, W. SCOTT KEMPER, and JOHN ROSS, Jr.

Using the relations at end-systole between left ventricular pressure, chamber dimensions, and regional left ventricular wall thickness (ultrasonic dimension gauges), overall and regional left ventricular function were studied during progressive coronary stenosis in conscious dogs. During regional ischemia, the end-systolic pressure-diameter relation shifted progressively, suggesting a global decrease in ventricular contractility. However, the end-systolic points relating left ventricular wall thickness in the ischemic region to end-systolic left ventricular pressure revealed the regional nature of the abnormality, showing a progressive displacement to the left of the control point, whereas there was no significant displacement of this relation in the control region. There was a progressive increase at end-systole in an index of regional wall stress. Regional end-systolic wall thickness-pressure relations provide a new index for defining the regional contractile state of the left ventricular myocardium. This index is potentially load-independent and may have echocardiographic application.

1759 First Ultra-Short-Acting Beta-Adrenergic Blocking Agent: Its Effect on Size and Segmental Wall Dynamics of Reperfused Myocardial Infarcts in Dogs

RÜDIGER LANGE, ROBERT A. KLONER, and EUGENE BRAUNWALD

Beta-adrenergic blocking agents have an established role in the treatment of myocardial ischemia, but precipitation of adverse effects may restrict their use in some patients with acute myocardial infarction or in patients undergoing coronary bypass surgery. ASL-8052 is a new cardioselective ultra-short–acting beta blocker which allows abolition of beta blockade in animals within 16 minutes on termination of an intravenous infusion. The authors investigated the effect of ASL-8052 on myocardial infarct size, regional myocardial wall function, and hemodynamic function during a 3-hour experimental occlusion of the left anterior descending coronary artery followed by 3 hours of reperfusion in dogs. After 3 hours of reperfusion, the incidence of myocardial tissue necrosis, as a function of the in vivo area at risk, was significantly lower in ASL-8052–treated (48 ± 7%) than in control (73 ± 6%) dogs ($p < 0.025$). During the early hours of reperfusion, functional deterioration occurred in control dogs but not in treated dogs. During the occlusion period, infusion of ASL-8052 caused a decrease in heart rate of 22 ± 3% ($p < 0.001$) and of the first derivative of left ventricular pressure of 22 ± 4% ($p < 0.05$). Upon reperfusion, control dogs exhibited an increase in heart rate of 26 ± 1% ($p < 0.05$). In treated dogs, heart rate did not change. Hence, infarct size, reperfusion tachycardia, and myocardial wall asynergy were reduced in ASL-8052–treated dogs. A potential advantage of this agent is that its short duration of action would allow rapid reversal of beta blockade if adverse effects developed.

1768 Sympathetic Denervation Limited to a Region of Acutely Ischemic Canine Myocardium Increases Excitability Threshold and Duration of Bipolar Electrograms

JAMES B. MARTINS, THOMAS M. MUELLER, and DOUGLAS P. ZIPES

This study determines the direct effects of sympathetic denervation on excitability threshold and bipolar electrograms in acutely ischemic myocardium. Regional denervation was performed by application of phenol to the epicardium surrounding the ischemic zone in order to eliminate the possible hemodynamic effects that global cardiac denervation may exert on the ischemic zone. Regional denervation increased the peak excitability threshold and prolonged the duration of bipolar electrograms in epicardium and endocardium. Phenol application did not alter aortic pressure, ischemic wall motion (sonomicrometer technique), or ischemic zone blood flow (microsphere technique). Thus acute sympathetic denervation when limited to ischemic myocardium increases the peak excitability threshold and concomitantly prolongs the duration of bipolar electrograms.

1775 Transvenous Ablation of the Atrioventricular Conduction System in Dogs: Electrophysiologic and Histologic Observations

GUST H. BARDY, RAYMOND E. IDEKER, JACK KASELL, SETH J. WORLEY, WILLIAM M. SMITH, LAWRENCE D. GERMAN, and JOHN J. GALLAGHER

The correlation of histologic and electrophysiologic findings in dogs undergoing transvenous ablation of atrioventricular (AV) conduction has not been described. The creation of complete AV block in 10 dogs was attempted by delivering a direct-current shock transvenously through a standard tripolar electrode catheter. After 1 shock, all dogs were in complete AV block refractory to isoproterenol and atropine. Four weeks later, 5 dogs remained in complete AV block, 1 had first-degree block, and 4 had resumed normal AV conduction. Although temporary heart block occurred in each animal, chronic interruption of AV conduction was more difficult. Catheter location, atrial and His bundle electrogram relations, and the electrode used for delivery of energy were factors determining the effectiveness of this technique.

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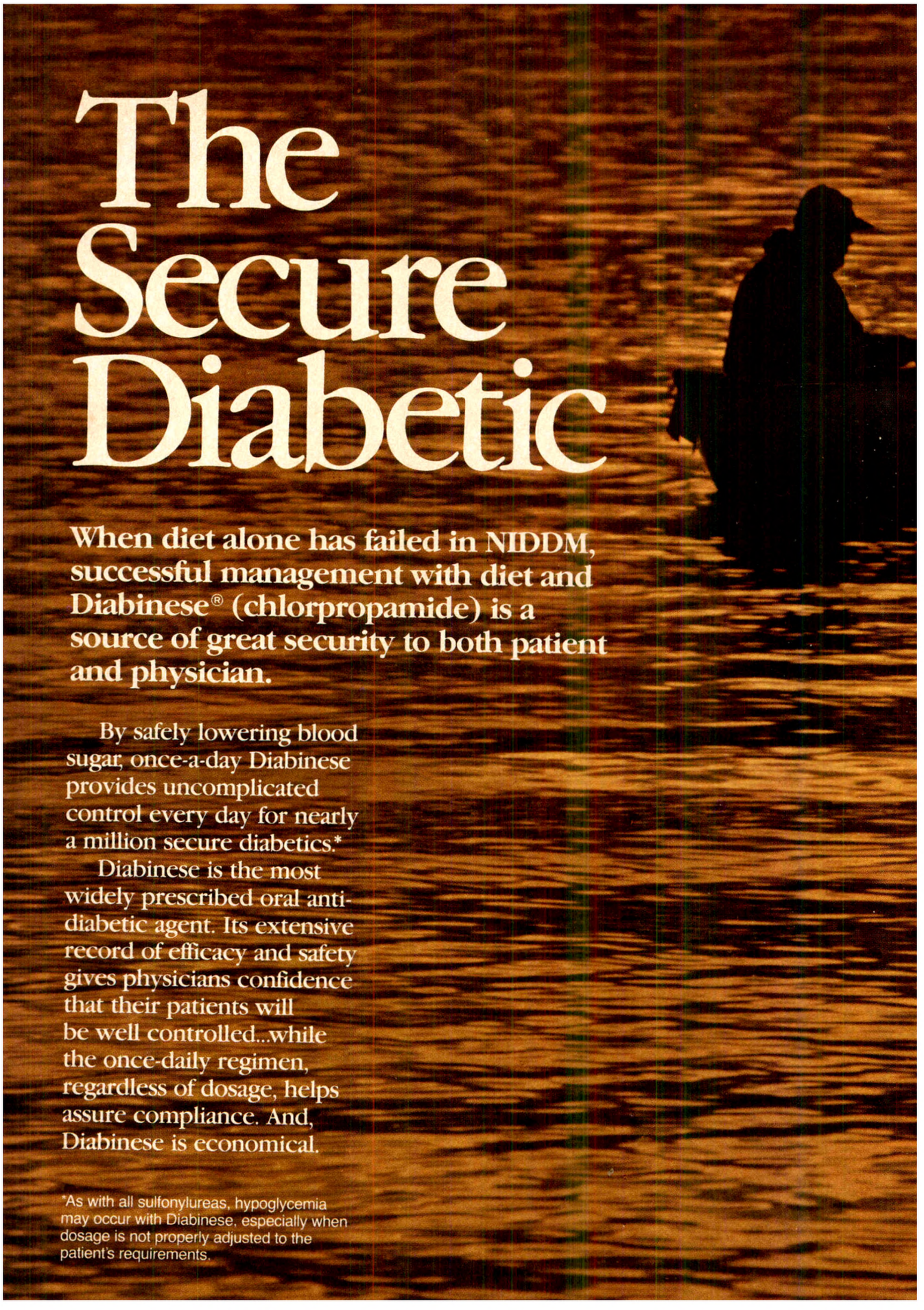
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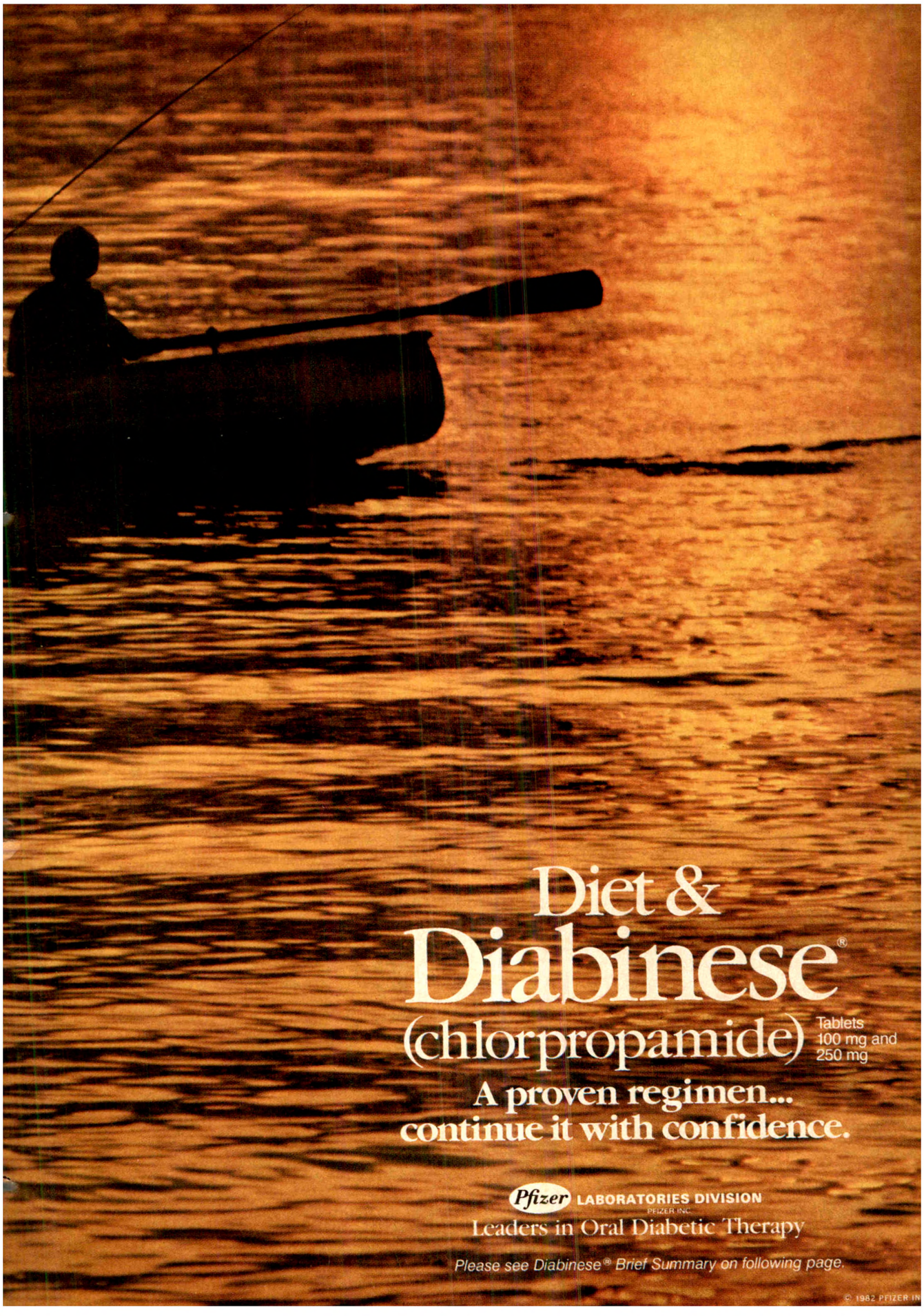
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Contraindications: Diabinese is not indicated in patients having juvenile or growth-onset diabetes mellitus, severe or unstable "brittle" diabetes, and diabetes complicated by ketosis and acidosis, diabetic coma, major surgery, severe infection, or severe trauma. Diabinese is contraindicated during pregnancy. Serious consideration should be given to the potential hazard of its use in women of childbearing age who may become pregnant.
Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.
Precautions: Use chlorpropamide with caution with barbiturates, in patients with Addison's disease or in those ingesting: alcohol, antibacterial sulfonamides, thiazides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors. Adequate dietary intake should be assured in all patients using Diabinese.
Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HERE, INSULIN IS INDISPENSABLE.
HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED. (SEE ADVERSE REACTIONS.) IN INSTANCES OF CONCOMITANT USE WITH INSULIN, PATIENTS SHOULD BE CAREFULLY MONITORED.
Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, nausea, vomiting and gastrointestinal intolerance; weakness and paresthesias.
Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. They occur characteristically during the first six weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug. The more severe manifestations may require other therapeutic measures, including corticosteroid therapy. Diabinese should be discontinued promptly when the development of sensitivity is suspected.
Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPIENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.
Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.
Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.
BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG REQUIRE CLOSE SUPERVISION FOR A MINIMUM PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.
Rare cases of phototoxic reactions have been reported.
Edema associated with hyponatremia has been infrequently reported. It is usually readily reversible when medication is discontinued.
Dosage: The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally, cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED. The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of Diabinese, in the range of 100 to 125 mg daily.
After five to seven days following initiation of therapy, dosage may be adjusted upward or downward in increments of 50 to 125 mg at intervals of three to five days. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. Maintenance doses above 750 mg daily should be avoided.
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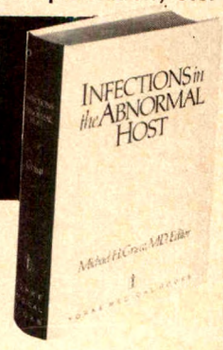

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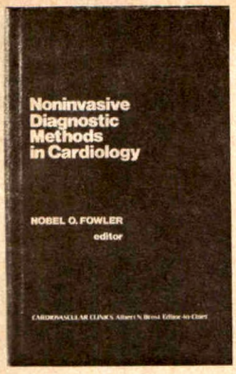

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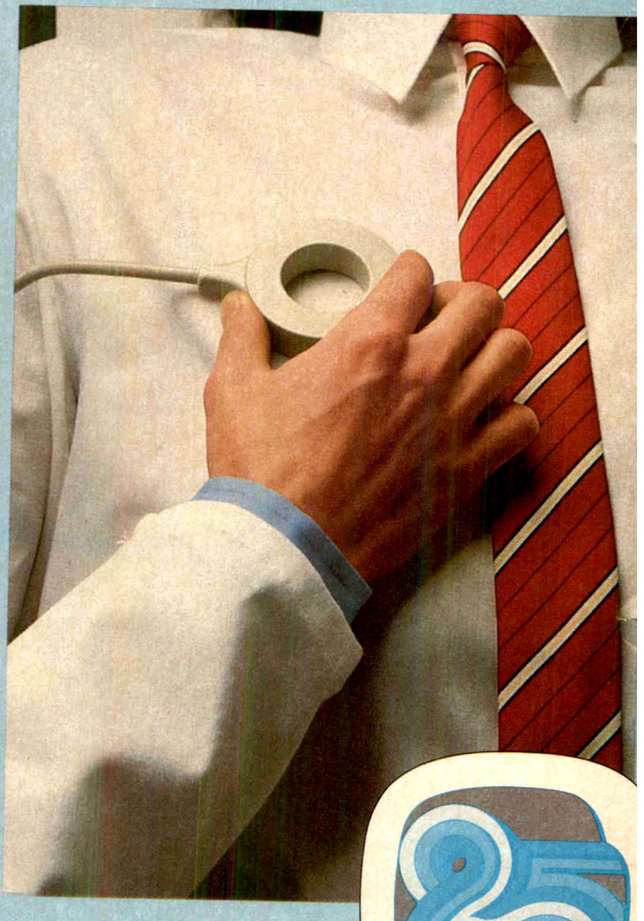

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resulting from surgical procedures could be extrusion of t generator, infection, fluid accumulation etc.

Stimulation of muscles adjacent to the pulse generator pocket may occur in the case of a unipolar lead system.

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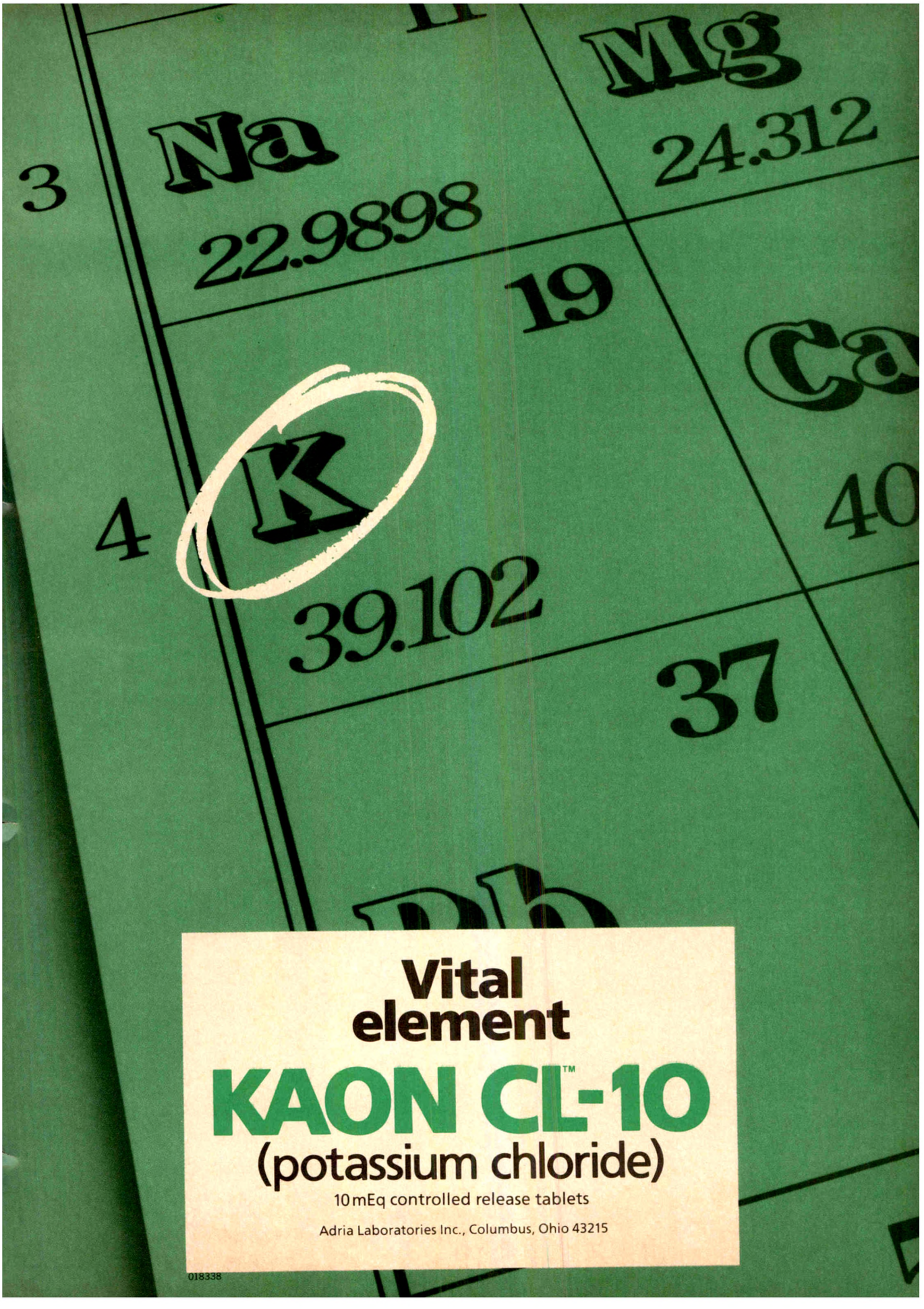

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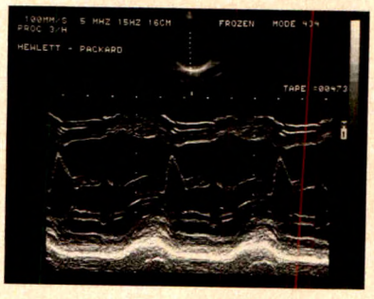

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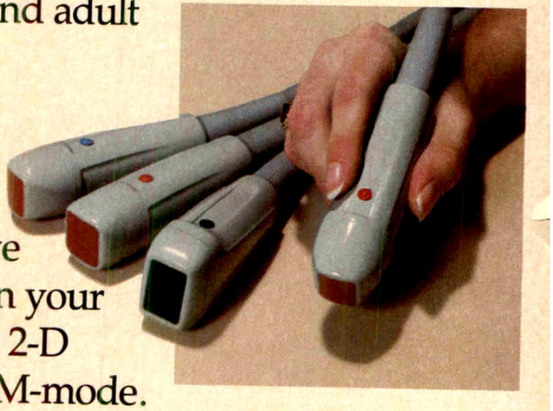

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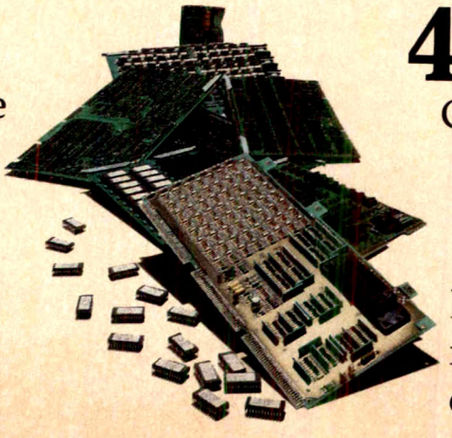

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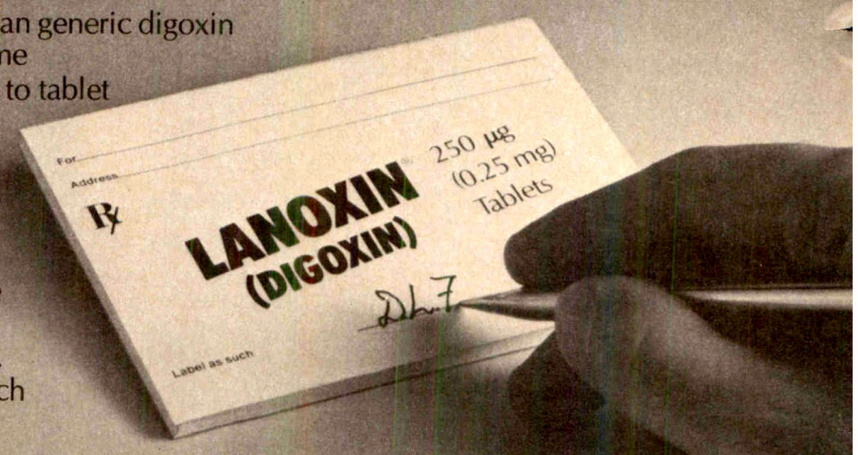

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VOLUME 51

CORONARY HEART DISEASE

Intracoronary Thrombolysis in Acute Myocardial Infarction: An Attempt to Quantitate Its Effect by Comparison of Enzymatic Estimate of Myocardial Necrosis With Left Ventricular Ejection Fraction

FRANZ SCHWARZ, MD, ANDREAS FAURE, MD, HUGO KATUS, MD, KLAUS VON OLSHAUSEN, MD, MANFRED HOFMANN, MD, GERHARD SCHULER, MD, JOACHIM MANTHEY, MD, and WOLFGANG KÜBLER, MD

The quantity of myocardium was estimated that can be salvaged by reperfusion of acute transmural myocardial infarction (MI). Serial analysis of serum creatine kinase (CK) activity was carried out in 41 consecutive patients with acute MI who underwent intracoronary thrombolysis. Enzymatic estimate of MI size was calculated using an average (method A) and an individually determined elimination constant (method B). Left ventricular ejection fraction 4 weeks after successful thrombolysis (cineangiogram) correlated inversely with MI size (method A: $r = -0.85$, method B: $r = -0.76$; both $p < 0.001$). Patients with recanalization within 4 hours after the onset of symptoms were assembled in group A_1 ($n = 13$, early reperfusion), and patients with successful recanalization after 4 hours in group A_2 ($n = 16$, late reperfusion). Group B consisted of 12 patients without reperfusion. MI size in group A_1 was 21 CK-g-Eq (method A) and 23 CK-g-Eq (method B), in group A_2 50 CK-g-Eq (method A) and 54 CK-g-Eq (method B), and in group B 73 CK-g-Eq (method A) and 63 CK-g-Eq (method B). Mean values in group A_1 were lower than in group A_2 and group B ($p < 0.05$). It is concluded that MI size was significantly reduced to about one third after early reperfusion as compared with no reperfusion. In contrast, MI size was not significantly reduced after late reperfusion.

The salvage of myocardium after coronary artery reperfusion in acute transmural myocardial infarction (MI) is critically dependent on the duration of coronary artery occlusion.[1] Non-surgical reperfusion has been established by use of intracoronary thrombolysis with streptokinase infusion in patients with acute MI.[2] The effect of the duration of ischemia on contraction of MI area has been studied,[3] but the effect on the enzymatic estimate of MI size has not clearly been defined. The present study quantitates the effects of early reperfusion (<4 hours after onset of symptoms) and late reperfusion (>4 hours after onset of symptoms) by the use of MI size.

From the Abteilung Innere Medizin III der Medizinischen Universitätsklinik, Heidelberg, West Germany. This study was supported by a grant from the Deutsche Forschungsgemeinschaft, Bonn Bad Godesberg, within the SFB 90 Kardiovaskuläres System, University of Heidelberg, Heidelberg, West Germany. Manuscript received November 24, 1982; revised manuscript received February 18, 1983, accepted February 22, 1983.

Address for reprints: Franz Schwarz, MD, Abteilung Innere Medizin III, Medizinische Universitätsklinik, Bergheimer Strasse 58, 6900 Heidelberg, West Germany.

Methods

Patients: Forty-one consecutive patients with acute MI in whom intracoronary infusion with streptokinase was performed to recanalize the obstructed coronary artery were studied. The diagnosis of acute MI was based on (1) acute chest pain lasting >30 minutes, (2) persistent S-T segment elevation (>2 mm in ≥3 leads of the standard 12-lead electrocardiogram) lasting >30 minutes and progressing to new Q waves. Not accepted to the study were (1) patients with symptoms >6 hours at entry into the coronary care unit, (2) patients with recurrent MI of a perviously infarcted area, and (3) patients >75 years of age. No patient was excluded from

invasive therapy because of poor hemodynamic condition. The clinical class was evaluated immediately after entry into the coronary care unit.[4]

Cardiac catheterization: Patients were studied with selective coronary arteriography using the femoral percutaneous technique. Heparin, 7,500 U intraarterially, and prednisolone, 250 mg intravenously, were given to prevent allergic reactions to streptokinase. Diazepam and morphine sulfate were administered when necessary. Selective arteriography of the right and left coronary artery (by manual injection) was performed in 6 projections, including 3 hemiaxial projections, after left ventricular (LV) cineangiography. When coronary occlusion was clearly visualized, intracoronary injection of 0.2 to 0.4 mg of nitroglycerin was performed to exclude spastic occlusion; thereafter, continuous infusion of streptokinase (2,000 U/min) was started with the coronary catheter in the coronary ostium. Injections of contrast material were repeated every 15 minutes and the infusion was stopped 15 minutes after reperfusion. If the coronary vessel was not reopened after infusion of 200,000 U of streptokinase, the attempt was given up. Successful reperfusion was defined as reopening of the occluded vessel with good runoff or markedly improved runoff in cases of subtotal occlusion. After the invasive diagnostic and therapeutic maneuvers, the patient was transferred to the coronary care unit.

Patient care: Patients were treated with bedrest. Administration of intravenous heparin was begun according to thrombin time to achieve therapeutic anticoagulation (prolongation of thrombin time 2 to 3 times the normal value). This therapy was followed by oral phenprocoumon. Patients left the coronary care unit after 4 to 5 days. LV and coronary angiography was repeated in 35 patients 4 weeks after acute MI. Monoplane LV cineangiography was performed in the 30° right anterior oblique projection (40 ml of Urografin® 76, 35-mm film, 50 frames/s, Philips dual-field 9–5–inch image intensifier system). Patients were discharged from the hospital 1 day later.

Enzymatic estimate of myocardial necrosis (MI size): Blood samples were taken from the patients immediately after admission and thereafter at hourly intervals for 12 hours, at intervals of 2 hours up to 20 hours, at intervals of 4 hours up to 48 hours, and at intervals of 12 hours up to 80 to 100 hours. Serum creatine kinase (CK) activity was determined by the enzymatic method, using a commercial monotest and a Centrifichem autoanalyzer.[5] Normal range of CK in serum is up to 80 U/liter.[5] Repeated measurements of serum CK activity from the same samples correlated closely: $y = -3.9 \pm 1.03\,x$, where y equals the second determination and x equals the first determination, $r = 0.95$. From the serum CK curves, the area under the curve was calculated by segmented approximation.[6] The elimination constant was determined in each patient from the declining slope of the time-activity curve by linear regression analysis using a logarithmic scale for serum CK activity.[7] Individual appearance curves were calculated and included the quantity of CK activity normally lost by excretion. Finally, MI size was calculated according to Sobel et al[8] with the use of the constants suggested by Bleifeld et al[6] with an average elimination constant of 0.06 (method A) as well as with individually determined elimination constants (method B).

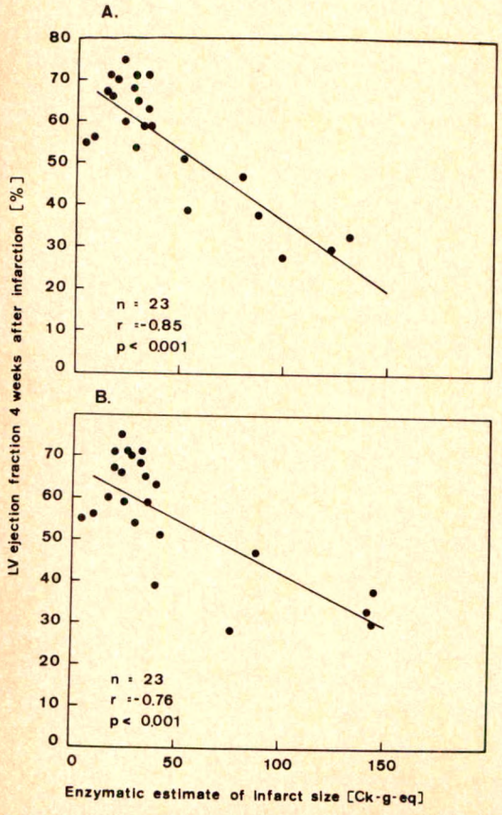

FIGURE 1. Inverse linear relations between enzymatic estimate of infarct size and left ventricular ejection fraction 4 weeks after successful thrombolysis. **A,** method A (enzymatic estimate calculated with an elimination constant of 0.06); **B,** method B (enzymatic estimate calculated with individual elimination constants).

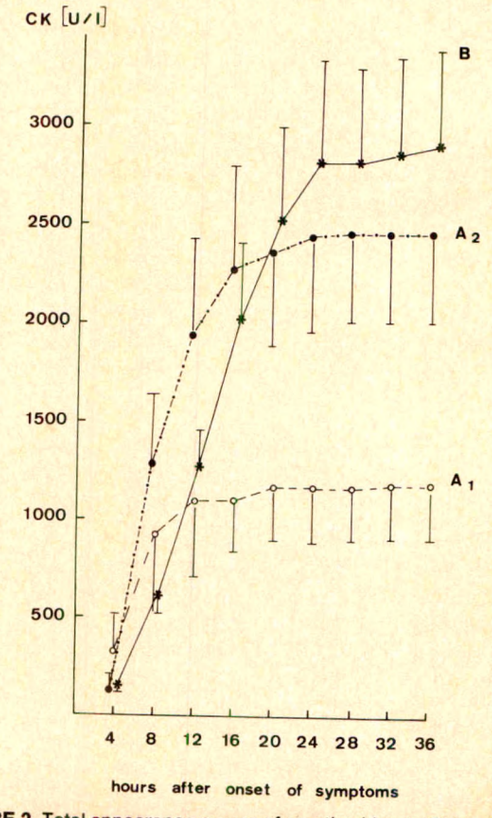

FIGURE 2. Total appearance curves of creatine kinase (CK) activities which were averaged at 4 hourly intervals for the 3 groups: group A_1 = reperfusion within 4 hours; group A_2 = reperfusion after 4 hours; group B = no reperfusion. The plateau of the curve of group A_1 was lower than that of both other groups ($p < 0.05$).

MB fraction of CK was determined by radioimmunoassay of our own design (HK). The interassay variations are <10%. The peak values of CK activity and the MB fraction were compared in 24 patients with acute MI, and a close correlation was obtained between both measurements (r = 0.85).

Analysis of angiograms: The angiograms were interpreted independently by 2 experienced observers. From coronary arteriograms, obstructions were determined and collateral circulation to the distal vessel segment (infarct vessel before recanalization) was carefully noted. Coronary anatomy was scored as suggested by Gensini[9] and scores were calculated for all coronary vessels and for the MI vessel. The Gensini score evaluates (1) the geometrically increasing severity of coronary lesions (based on the nonlinear correlation between percentage stenosis and coronary flow), (2) the significance of their location (estimate of the size of the perfusion area), and (3) the modifying influence of the coronary collateral vessels. Estimates of the severity of coronary anatomy by 2 observers correlated highly (r = 0.90, n = 60). From the LV angiograms, end-diastolic, end-systolic, and stroke volumes were determined, and the ejection fraction (EF) was calculated.[10] The EF was measured by 2 experienced observers independently in 15 patients and comparison of data revealed a good correlation coefficient of 0.93.

Statistical analysis: For statistical analysis, the analysis of variance, the Student-Newman-Keuls test, and the chi-square procedure (Brandt-Snedecor) were used.[11] Differences were considered significant when p was <0.05. Mean values ± the standard deviation are given in the tables and the Results section. In Figure 2 the standard error of the mean is depicted.

TABLE I Clinical and Baseline Hemodynamic Characteristics

	Group A_1: Early Reperfusion	Group A_2: Late Reperfusion	Group B: No Reperfusion
Patients (n)	13	16	12
Age (yr)	57 ± 10	58 ± 8	53 ± 10
Sex, male	10	14	12
Killip class I before therapy	12	13	10
Killip class II before therapy	1	3	2
Anterior infarction	6	6	5
Inferior infarction	7	10	7
Previous infarction	0	2	2
Gensini score (all vessels)	47 ± 19	50 ± 27	60 ± 24
Gensini score (infarct vessel)	41 ± 18	39 ± 21	46 ± 19
Infarct vessel			
Left anterior descending branch	6	6	5
Left circumflex branch	2	3	2
Right coronary artery	5	7	5
Angiographically visible collaterals to infarct	4	7	4
Left ventricular ejection fraction before therapy (%)	52 ± 10	46 ± 11	45 ± 14
Interval (h) between onset of symptoms and catheterization	2.9 ± 0.7*†	4.3 ± 0.8	3.8 ± 0.7
Interval (h) between onset of symptoms and reperfusion	3.1 ± 0.6	5.1 ± 0.7	. . .
Serum CK activity before therapy (U/liter)	41 ± 14	55 ± 45	45 ± 14
Dose of streptokinase ($\times 10^3$ IU)	113 ± 46*†	167 ± 44	173 ± 48
Direct-current shock during acute MI	1	3	2
Recurrence of MI within 4 weeks	3	2	0
Cardiogenic shock	0	0	2
Intraaortic balloon pump	0	0	1
Beta-adrenergic agonists	0‡	2	4
Diuretics	3	6	6
Digitalis	2	6	3
Nitrates	6	5	5
Beta-adrenergic blockade	7	8	5
Calcium-channel blockade	3	4	3

* p <0.01 versus group A_2; † p <0.01 versus group B; ‡ p <0.05
... group B; CK = creatine kinase; MI = myocardial infarction.

Results

MI size versus LVEF 4 weeks after thrombolysis (Fig. 1): Data on MI size and LVEF 4 weeks after successful thrombolysis (as a quantitative measure of LV dysfunction in the chronic stage of MI) were compared. Patients who had previous MI were excluded from the comparison.[12] Significant close inverse linear correlations were obtained (Fig. 1).

To quantitate the effect of early and late reperfusion on MI size, the following 3 groups were established: 13 patients with successful recanalization of the MI vessel <4 hours after the onset of symptoms were assembled in group A_1, 16 patients with recanalization after >4 hours in group A_2 and 12 patients with unsuccessful attempts to recanalize in group B.

LVEF 4 weeks after acute MI was 62 ± 9% in group A_1 (n = 10), 52 ± 16% in group A_2 (n = 13), and 43 ± 13% in group B (n = 9). The mean values in group A_1 and group B differed significantly (p <0.05), whereas differences between groups A_1 and A_2 as well as A_2 and B were not significant (p >0.05). Patients with reocclusion of the MI vessel (groups A_1 and A_2) were excluded from this comparison.

Quantification of the effect of early and late reperfusion and comparison with no reperfusion (Fig. 2): The age of the patients, sex, Killip class at entry into the coronary care unit, the number of anterior and inferior MI, the number of previous MI, baseline Gensini score for all coronary vessels, Gensini score for the MI vessel, localization of MI vessel, collateral supply to MI vessel, baseline EF, and serum CK activity were comparable among the groups (Table I). The interval between the onset of symptoms and recanalization was 3.1 hours in group A_1 and 5.1 hours in group A_2. The time between the onset of symptoms and the start of catheterization was shorter in group A_1 than in both other groups (Table I). The dose of intracoronary streptokinase was smaller in group A_1 than in groups A_2 and B. In group A_1, 12 of 13 patients had total occlusion of the MI vessel and 1 patient had subtotal occlusion with poor runoff. In group A_2, 14 of 16 patients had total occlusion and 2 patients had subtotal occlusion before therapy.

Table II lists the different time intervals between the onset of symptoms and peak CK activity, respectively, the time at which 80% of plateau of total CK activity was reached. The values were significantly lower in groups A_1 and A_2 as compared with group B. The plateau of total appearance of CK activity was significantly lower in group A_1 than in both other groups. Figure 2 illustrates average CK values (appearance curves) at 4 hourly intervals in the 3 groups. The elimination constants of CK activity from serum did not differ significantly among groups (Table II). MI size (Table II) was lower in group A_1 than in both other groups. In contrast,

TABLE II Enzymatic Estimates of Infarct Size

	Group A_1: Early Reperfusion	Group A_2: Late Reperfusion	Group B: No Reperfusion
Peak serum CK activity (U/liter)			
Mean ± SD	983 ± 1,104	1,756 ± 1,463	2,021 ± 1,431
Range	166–4,338	408–4,830	913–5,200
Interval (h) between onset of symptoms and peak CK activity			
Mean ± SD	12 ± 5*	14 ± 4*	19 ± 6
Range	5–16	7.5–20	12.5–33
Plateau value of total appearance of CK (U/liter)			
Mean ± SD	1,191 ± 1,015†‡	2,459 ± 1,799	2,855 ± 1,710
Range	180–5,300	520–6,400	1,200–6,430
Interval (h) between onset of symptoms and time at which 80% of plateau of total CK appearance was reached			
Mean ± SD	11 ± 4*	14 ± 6‡	19 ± 5
Range	5.5–17	7.5–23	12–29
Individual elimination constant			
Mean ± SD	0.068 ± 0.015	0.064 ± 0.014	0.057 ± 0.022
Range	0.039–0.087	0.045–0.100	0.036–0.096
Enzymatic estimate of infarct size using method A (CK-g-Eq)			
Mean ± SD	21 ± 20*†	50 ± 39	73 ± 46
Range	2–79	8–131	27–164
Enzymatic estimate of infarct size using method B (CK-g-Eq)			
Mean ± SD	23 ± 22†,‡	54 ± 46	63 ± 34
Range	2–88	11–145	19–129

* $p < 0.01$ versus group B; † $p < 0.05$ versus group A_2; ‡ $p < 0.05$ versus group B; CK = creatine kinase; SD = standard deviation.

MI size in group A_2 was not different from that in group B.

Hospital course: Patients were hospitalized for 4 weeks after acute MI. Recurrence of MI by clinical or enzymatic criteria, or both, was observed in 3 patients in group A_1 and in 2 patients in group A_2 during the hospital course. Complications of intracoronary streptokinase were minor bleeding at the puncture site in 5 patients, and gastrointestinal bleeding requiring blood transfusions in 1 patient. No patient in group A_1 and A_2 but 3 patients in group B died during their hospital course.

The drugs used during acute MI and during the hospital course are listed in Table I. No significant differences existed between groups except in the use of beta-adrenergic agonists which were more often used in group B than in group A_1.

Discussion

The data in the present study reveal that early reperfusion (<4 hours after the onset of symptoms [group A_1]) reduces the MI size to about one third of that observed in patients without recanalization of the MI vessel (group B). In contrast, reperfusion after periods >4 hours (group A_2) had little effect on MI size. Furthermore, group A_1 patients had a significantly smaller MI size than did those in group A_2.

The size of the MI is determined by (1) the duration of ischemia,[1] (2) the residual flow to the ischemic area[13] through collateral vessels, and (3) the size of the perfusion area of the MI vessel (area at risk,[14]). In the present study the groups were comparable with regard to the MI vessel and angiographically visible collaterals to the ischemic area. Therefore, residual blood flow to the ischemic area can be assumed to be similar. The size of the perfusion area was estimated by the Gensini score which incorporates the size of the territory perfused by a coronary vessel; this score was similar among groups.

Validity of enzymatic estimate of MI size: MI size determined by analysis of total serum CK activity correlated closely to the pathologically measured MI size ($r = 0.93$) in 15 patients with acute MI studied by Bleifeld et al.[5] A more recent study by Grande et al[15] described highly significant correlations (r between 0.71 and 0.87) between MI size and myocardial necrosis (nitroblue tetrazolium staining and histologic study). Myocardial necrosis ranged between 5 and 160 g of tissue in the latter study,[15] therefore including even large MI. These studies confirm that MI size in patients with acute MI can be estimated with acceptable accuracy from serial analysis of total CK activity in serum. The influence of reperfusion and of streptokinase on myocardial CK release and degradation in serum is not yet fully understood. However, because streptokinase was used in all 3 groups, a systematic error can be excluded. In addition, the determination of CK activity and MB fraction showed a close correlation ($r = 0.85$) in the present study, thereby excluding the possibility of altered enzyme activity due to the therapeutic intervention.

In the present study, MI size was calculated by using an average elimination constant (method A) and by determining an individual elimination constant (method B). In the larger MI the elimination constant is easily determined from the monoexponential part of the plasma curve, but with the smaller MI the determination becomes less precise. The use of an average elimination constant is supported by the finding that

the elimination constants were similar in both large and small MI.[15] The elimination constant may vary among different individuals with a range of 0.036 to 0.096 in the present series: the mean value among reperfused patients was 0.067 and was similar to the value of 0.057 in nonreperfused patients (Table II). The results and conclusions in this study are independent of whether the elimination constant was assumed constant or determined individually.

LV function as measured by the EF 4 weeks after reperfusion correlated with MI size. We assumed that after 4 weeks the LVEF reflected the size of myocardial necrosis which was measured by MI size during acute MI. The close inverse correlation observed is an argument that enzymes reflect MI size even under conditions of reperfusion in man. A correlation of MI size and EF was not previously documented in patients with reperfusion in acute MI. Rogers et al[12] described a close inverse correlation ($r = -0.78$) between MI size and EF in patients with acute MI without reperfusion. Morrison et al[16] described a similar correlation ($r = -0.78$) when excluding patients with previous MI. In some rare cases with extensive right ventricular MI, the correlation was poor because of the excessive release of enzymes from the right ventricle.[16] Our findings in patients with reperfusion of acute MI are in accordance with these studies. Extensive right ventricular MI, a relatively rare complication of inferior MI,[17] was not observed after reperfusion in the present series. It has to be considered that reperfusion in man incorporates restricted reflow through residual coronary stenosis into infarcted and ischemic tissue. Thus, although the enzymatic method may have limitations,[18–20] our data support the conclusion that in patients with thrombolysis enzymes can be used to estimate MI size.

Limitations of enzymatic method for determination of MI size: The enzymatic method has certain limitations: (1) subendocardial MI, scattered MIs, and small transmural MIs release a greater amount of CK into the blood compared with large MIs.[18–20] Therefore, the size of a large MI may become underestimated because the serum entry ratio of CK decreases as the size of the necrosis increases in the experimental animal.[19,20] Two studies of the same group[19,20] have investigated the problem of a variable serum entry ratio of CK after experimental coronary artery ligation in the dog. Two different conclusions have been reached: the first study[19] could not distinguish small from large histologic MI by serum enzyme measurements; the second study[20] described a linear relation with the coefficient $r = 0.75$ between enzymatic and pathologic MI size. The discrepancy between both studies was explained by technical reasons (interval of blood sampling and location of coronary ligation). The latter study finally concluded that MI size underestimated histologic necrosis in large experimental MI to some extent.[20] Whether a similar underestimation occurs in MI in human subjects is unknown: a linear relation between MI size and histologic MI was described in man.[6,15] Coronary artery reperfusion during acute MI causes greater release of enzymes per gram of infarcted tissue than does permanent coronary occlusion.[21,22] Vatner et al[21] measured MI size in dogs reperfused after 1 or 3 hours of coronary occlusion. The average amount of CK in the blood over 24 hours was higher after reperfusion as compared with permanent occlusion (per gram of pathologically infarcted tissue). Nevertheless, a good correlation existed between MI size and the pathologically determined extent of MI ($r = 0.90$). These findings justify comparison of MI size between groups with reperfusion as in the present study (groups A_1 and A_2). The data revealed a shorter time interval between the onset of symptoms and peak serum CK activity in groups with reperfusion as compared with the group without reperfusion. This finding may be due to a washout effect[21] and may produce some overestimation of MI size in groups A_1 and A_2. The reduction in myocardial necrosis in the present study should be even greater than that in groups A_1 and A_2 as compared with group B.

Clinical implications: A beneficial effect of early reperfusion on MI size and on LVEF was shown compared with patients with late reperfusion and without reperfusion. Early reperfusion reduced MI size to about one third of that seen in the group without reperfusion. Late reperfusion seemed to have only a minor effect, although it cannot be excluded that some overestimation of MI size due to enhanced enzyme washout occurred in this group. The duration of ischemia is a major determinant of therapeutic success of reperfusion of acute MI.

The present study is a retrospective analysis and quantitates the amount of myocardium that can be salvaged by early reperfusion in human subjects. The question being investigated was whether early reperfusion limits MI size as compared with no reperfusion. A randomized study may answer the question of whether streptokinase therapy is superior to conventional therapy. However, we are not aware of a method for randomization that could answer the question of whether early reperfusion limits MI size.

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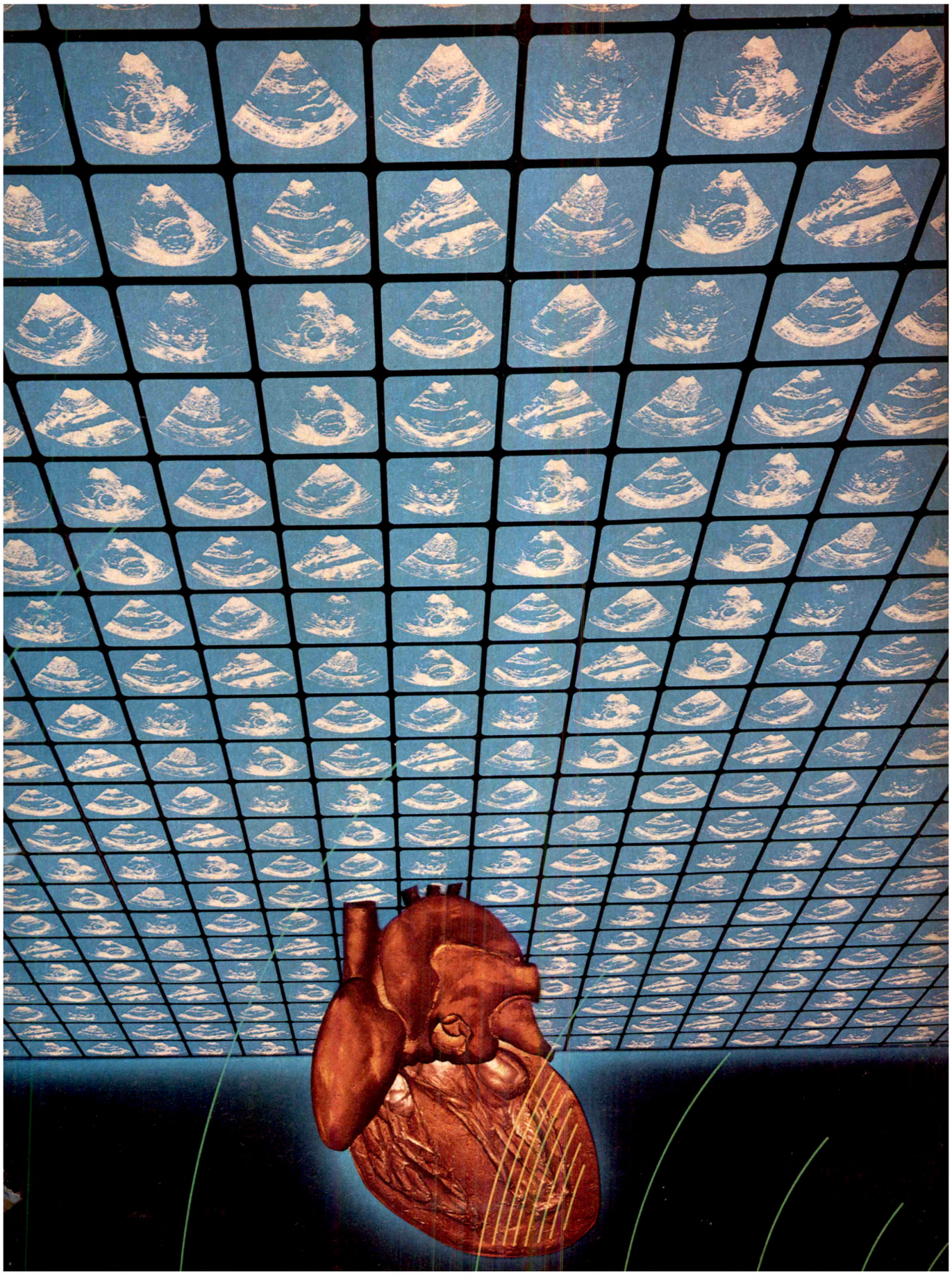

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Pulse duration/ output current, ms/mA (each channel)	0.2/2 0.3/3 0.4/4	0.5/5 0.6/6 0.8/8	1.0/10 2.0/12
A-V delay, ms	75, 100, 125, 150, 175, 200, 250		
Refractory, ms (each channel)	250, 300, 350, 400, 500		
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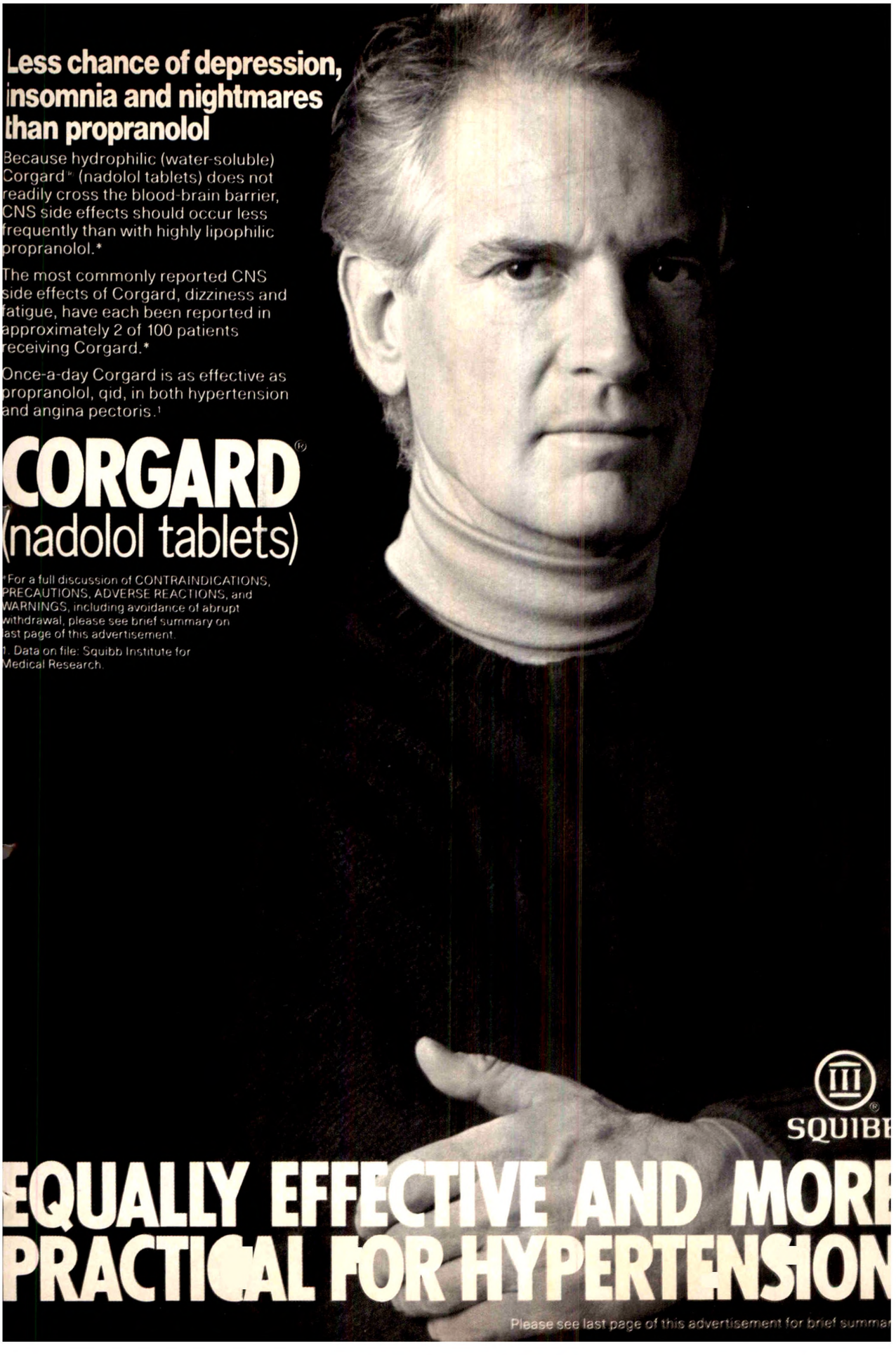
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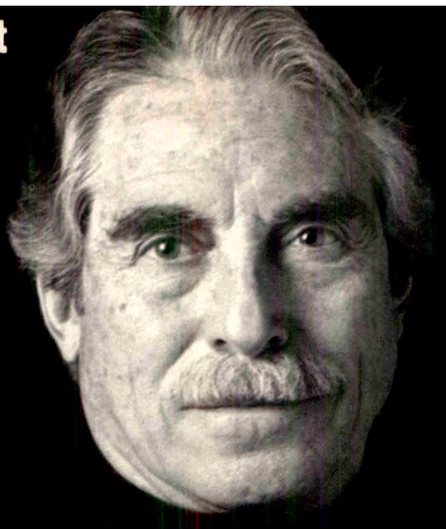

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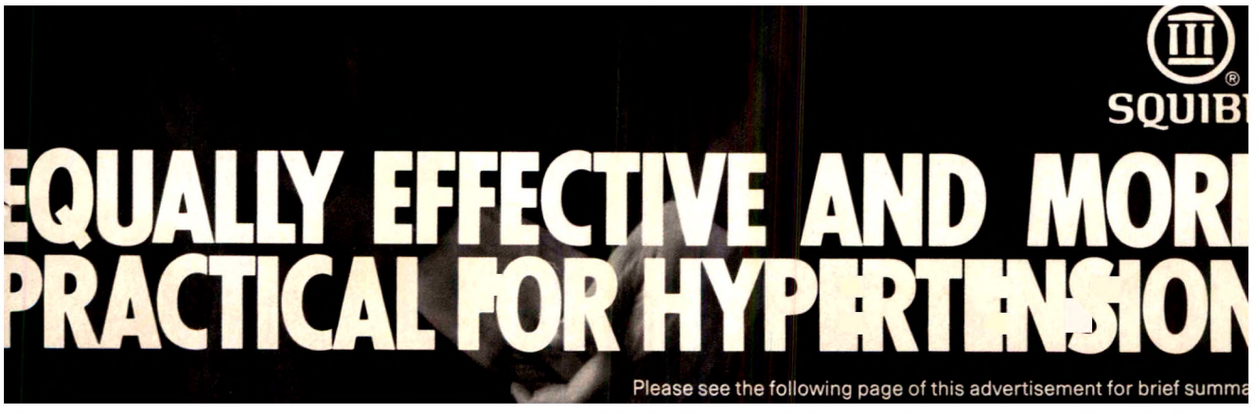
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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embry fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times (on a mg/kg basis) than maximum indicated human dose; no teratogenic potenti seen in any of these species. There are no well-controlled studies in pregnant w therefore, use nadolol in pregnant women only if potential benefit justifies potenti to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in humar Because many drugs are excreted in human milk, exercise caution when nad administered to a nursing woman. Animal studies showed that nadolol is found milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been establish

ADVERSE REACTIONS: Most adverse effects have been mild and transient an rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per r occurs commonly, and heart rates below 40 beats per minute and/or sympt bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral va insufficiency, usually of the Raynaud type, have occurred in approximately 2 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have occurred in about 1 of 100 patients. Single instances of first degree and third degree block have been reported; intensification of AV block is a known effect of beta-bl (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Ner System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresth sedation, and change in behavior reported in approximately 6 of 1000 pa **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patient CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, dia abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, ey skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; c nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug us not clear, sleep disturbances have been reported. The oculomucocutaneous sync associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other adrenergic blocking agents have not been reported with nadolol, they shou considered potential adverse effects of nadolol. **Central Nervous System —** reve mental depression progressing to catatonia; visual disturbances; hallucinations; an reversible syndrome characterized by disorientation for time and place; short memory loss, emotional lability with slightly clouded sensorium; decreased perform on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; isch colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocyto purpura. **Allergic —** fever combined with aching and sore throat; laryngosp respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's dis erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodia In addition to gastric lavage, employ the following measures as appropriat determining duration of corrective therapy, take note of long duration of effect of na

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been rep that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (Th evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophy derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronou slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most pat respond to 160 mg or less daily). If treatment is to be discontinued, reduce do gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 8 increments until optimum blood pressure reduction is achieved; usual maintenance is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package inse dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per t in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. 40 mg and 80 mg tablets are also available in convenience packages containing 4 b cards of 7 tablets each.

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Coronary Dilatory Capacity in Idiopathic Dilated Cardiomyopathy: Analysis of 16 Patients

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Hemodynamic function and overall coronary blood flow (argon technique) were measured in 16 patients with idiopathic dilated cardiomyopathy (IDC) and in 12 patients without detectable heart disease (control subjects) referred for precordial pain. In patients with IDC, coronary blood flow was normal at rest (78 ± 17 ml/100 g·min versus 78 ± 9 in control subjects). During maximal inducible coronary vasodilation (dipyridamole, 0.5 mg/kg), coronary blood flow was significantly reduced (142 ± 38 ml/100 g·min versus 301 ± 64 in control subjects; p <0.001). Consequently, obtainable minimal coronary resistance was increased in IDC (0.54 ± 0.20 mm Hg/ml/100 g·min versus 0.23 ± 0.04 in control subjects; p <0.001). In patients with IDC, left ventricular (LV) end-diastolic pressure was significantly increased (19 ± 11 mm Hg versus 6 ± 3 in control subjects; p <0.005), and the LV ejection fraction was diminished (36 ± 11% versus 72 ± 3% in control subjects; p <0.001). In patients with IDC, LV end-diastolic pressure correlated significantly with the obtained minimal coronary resistance after application of dipyridamole (r = 0.85; p <0.001). LV catheter biopsy specimens revealed no alterations in myocardial microvasculature. Thus, coronary dilatory capacity is impaired in patients with IDC, due partially to an increase in extravascular component of coronary resistance.

Patients with idiopathic dilated cardiomyopathy (IDC) frequently have chest pain suggestive of ischemic heart disease, despite the presence of normal coronary arteries. There have been only a few studies of coronary circulation in patients with IDC, and these have yielded conflicting results.[1–6] Coronary dilatory capacity has not been systematically evaluated in patients with IDC, although a possible inadequacy of myocardial perfusion might be involved. Therefore, coronary blood flow was measured by an improved inert gas technique at rest and during pharmacologically induced coronary vasodilation leading to an exhaustion of coronary dilatory capacity.

Methods

Group A (control) consisted of 12 patients (7 male and 5 female, mean age 45 ± 9 years) without detectable heart disease. These patients had recurrent atypical chest pain and were referred for coronary arteriography to exclude an organic cause of the symptoms. All patients in this group had normal electrocardiograms at rest and during exercise and normal coronary and left ventricular (LV) angiograms.

Group B consisted of 16 patients (14 male and 2 female, mean age 42 ± 9 years) with clinical and angiographic evidence of IDC. The origin was unknown in all patients. None of these patients had valvular or coronary heart disease. Hemodynamic and angiographic data from patients in Groups A and B are given in Table I. All patients in Group B had an abnormal electrocardiogram with left bundle branch block (n = 8), right bundle block (n = 1), multifocal premature ventricular beats (n = 4), abnormal depression of the S-T segment in leads V_5 and V_6 (n = 4), and lack of R progression in leads V_2 and V_3 (n = 3). Sinus rhythm was present in all patients in Group B except Patient 14. They received premedication with 10 mg of oral diazepam and were in the fasting state.

Determination of coronary blood flow: Coronary blood flow was determined by the argon method after right and left-sided cardiac catheterization. Details on this method as well as its accuracy, which allows measurement of even high coronary flow rates of >300 ml/100 g·min, were reported previously.[7–12] The argon method represents an improved inert gas saturation technique. The patient spontaneously inspired a gaseous mixture (79% argon, 21% oxygen) over a period of 5 minutes. Simultaneously, arterial and coronary venous blood samples were continuously collected. Argon analyses were carried out by gas chromatography.

According to the formula of Kety,[13] coronary blood flow is proportional to tissue concentration of the indicator divided

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TABLE I Hemodynamic and Angiographic Data

Patient	Age (yr)	LVEDP (mm Hg)	HR (beats/min)		RAP (mm Hg)		PAP (mm Hg)		AOP Systolic (mm Hg)	
			R	D	R	D	R	D	R	D
Controls (C)										
1	51	4	79	76	2	2	9	11	120	105
2	40	3	84	98	2	2	8	8	130	130
3	43	9	74	95	3	2	11	11	120	105
4	55	4	68	108	3	3	—	—	135	105
5	31	8	82	135	3	3	11	10	125	115
6	44	12	65	82	4	3	15	13	135	130
7	52	5	60	68	3	3	—	—	120	100
8	50	6	95	102	3	2	12	13	130	110
9	50	7	62	71	2	2	10	9	115	90
10	41	10	82	90	3	2	12	11	95	95
11	29	8	59	114	3	3	10	9	115	105
12	57	6	66	89	2	2	10	11	125	100
Mean	44.8	6.5	73	94	2.8	2.4	11	11	122	108
± SD	8.7	2.8	11.3	19.2	0.6	0.5	1.8	1.8	10.5	8.6
p (R vs D)			<0.005		NS		NS		<0.001	
Idiopathic Dilated Cardiomyopathy (IDC)										
1	30	8	84	83	8	7	11	10	120	110
2	35	35	64	68	10	10	41	37	125	110
3	34	7	70	80	4	4	9	9	140	145
4	40	7	74	85	5	4	14	13	95	95
5	41	35	105	115	5	5	—	—	100	100
6	21	10	75	100	5	6	—	—	100	95
7	40	22	81	89	5	5	25	26	115	110
8	54	14	100	110	4	5	10	11	140	140
9	51	10	70	105	5	4	—	—	115	105
10	45	9	90	110	3	3	16	16	115	100
11	48	17	53	83	3	3	19	18	110	110
12	53	38	87	94	9	8	40	38	180	180
13	50	10	65	70	8	8	13	14	90	80
14	45	25	83	87	2	1	31	30	110	120
15	47	15	70	77	14	13	20	22	125	105
16	42	35	75	87	20	17	48	46	125	135
Mean	42.3	18.6	78	90	6.9	6.4	23	22	119	115
± SD	8.6	11.4	13.0	14.5	4.5	4.0	12.6	11.7	21.0	23.7
p (R vs D)			<0.001		NS		NS		NS	
p (C vs IDC)	NS	<0.005	NS	NS	<0.01	<0.01	<0.01	<0.01	NS	NS

AOP = aortic pressure; CBF = coronary blood flow; CR = coronary resistance; D = dipyridamole (0.5 mg/kg intravenously); HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; LV Mass = left ventricular mass; NS = not significant; PAP = mean pulmonary arterial pressure; R = resting conditions; RAP = mean right atrial pressure; Vcf = mean velocity of circumferential fiber shortening.

by the mean arteriocoronary venous difference of the indicator. Tissue concentration of the myocardium results from the coronary venous concentration at the end of the saturation period multiplied by the tissue partition coefficient of the indicator (argon = 1.1). Coronary resistance was calculated as follows: [Mean diastolic aortic pressure − mean right atrial pressure (mm Hg)]/[coronary blood flow (ml/100 g·min)].

Evaluation of maximal coronary vasodilation: Measurements of coronary blood flow were carried out under resting conditions and during maximal inducible coronary vasodilation. The latter was achieved by the intravenous injection of 0.5 mg/kg of dipyridamole, which was administered over a period of 10 minutes. Immediately thereafter, blood sampling was started.

Minimal coronary resistance of normal coronary vessels of the dog heart has been found to be approximately 0.20 mm Hg/ml/100 g·min.[14–16] Comparable values of minimal coronary resistance measured in control subjects after intravenous application of dipyridamole[10,11,17] demonstrate that maximal vasodilation can be achieved by dipyridamole infusion (0.5 mg/kg intravenously). In order to confirm that the dose of dipyridamole was adequate for induction of maximal coronary vasodilation in patients with IDC, in 5 of these patients coronary resistance was measured (1) after an initial infusion of dipyridamole (0.5 mg/kg over a period of 10 minutes), and (2) immediately after a second infusion of dipyridamole in the same dose. The minimal coronary resistance after the first infusion was 0.45 ± 0.08 mm Hg/ml/100 g·min; the respective value after the second infusion was 0.43 ± 0.07 mm Hg/ml/100 g·min (the values are not significantly different). This observation suggests that even in patients with IDC the minimal coronary resistance is achieved by dipyridamole in a dose of 0.5 mg/kg body weight.

Coronary and left ventricular angiography: Selective coronary arteriography was performed with multiple views of the right (at least 3 projections) and left (at least 5 projec-

TABLE I (continued)

Patient	AOP Diastolic (mm Hg) R	AOP Diastolic (mm Hg) D	CBF (ml/100 g·min) R	CBF (ml/100 g·min) D	CR (mm Hg/ml/100 g·min) R	CR (mm Hg/ml/100 g·min) D	LVEF (%)	Vcf (circ/s)	LV Mass (g/m^2)
Controls (C)									
1	65	55	85	241	0.87	0.26	68	1.23	84
2	85	85	82	333	1.05	0.25	71	1.48	70
3	70	60	79	382	0.98	0.18	77	1.51	102
4	70	55	91	324	0.85	0.18	72	1.27	62
5	80	80	91	348	0.97	0.23	73	1.56	66
6	80	75	77	301	1.10	0.27	70	1.28	60
7	80	50	71	206	1.13	0.27	73	1.26	64
8	75	60	85	237	0.95	0.27	77	1.62	57
9	65	55	64	261	1.28	0.23	71	1.22	78
10	60	60	66	411	0.98	0.17	68	1.18	71
11	70	65	75	324	1.06	0.20	69	1.32	80
12	80	60	71	244	1.16	0.27	78	1.65	80
Mean	73	63	78	301	1.03	0.23	72	1.38	73
± SD	8.6	10.8	9.0	63.6	0.12	0.04	3.5	0.17	12.7
p (R vs D)	<0.001		<0.001		<0.001				
Idiopathic Dilated Cardiomyopathy (IDC)									
1	70	60	96	143	0.80	0.41	43	0.59	150
2	70	65	44	65	1.70	1.00	24	0.32	—
3	75	80	95	200	0.95	0.46	40	0.61	77
4	45	50	92	134	0.54	0.37	42	0.70	105
5	70	60	88	98	0.80	0.61	28	0.27	85
6	65	65	50	150	1.34	0.43	46	0.67	109
7	65	75	91	120	0.86	0.64	49	0.88	101
8	85	85	88	201	1.08	0.47	42	0.65	82
9	70	65	57	170	1.28	0.41	44	0.65	91
10	60	50	93	145	0.81	0.38	43	0.63	81
11	70	60	64	144	1.17	0.47	33	0.49	137
12	110	100	64	168	1.95	0.68	29	0.33	154
13	60	40	89	186	0.62	0.28	53	1.02	118
14	65	65	84	137	0.89	0.55	18	0.26	111
15	70	60	88	126	0.74	0.48	21	0.29	243
16	80	90	65	90	1.15	0.94	27	0.47	185
Mean	71	67	78	142	1.04	0.54	36	0.55	122
± SD	13.3	15.2	17.5	38.0	0.37	0.20	10.7	0.22	45.7
p (R vs D)	NS		<0.001		<0.001				
p (C vs IDC)	NS	NS	NS	<0.001	NS	<0.001	<0.001	<0.001	<0.005

tions) coronary arteries, including hemiaxial projections. Intracardiac pressure were obtained by means of a fluid-filled catheter pressure transducer system. End-diastolic and end-systolic volumes, the ejection fraction, and mean velocity of circumferential fiber shortening were calculated from the monoplane angiogram in a 30° right anterior oblique projection. A representative measurement of LV wall thickness was made from right anterior oblique projection of the ventriculogram in end-diastole at the point approximately halfway between the apex and the aortic valve. LV muscle mass was calculated according to Rackley et al.[18]

Transarterial left ventricular endomyocardial biopsy: Using King's College bioptome and the St. Thomas' sheath,[19] biopsy specimens of 12 patients with IDC were taken from LV myocardium and immediately fixed by immersion with a 1.5% glutaraldehyde-1.5% formaldehyde mixture in 0.1 *M* phosphate buffer. The tissue was embedded and oriented in the block in such a way that endocardium, Purkinje fibers, and myocardium could be clearly identified by light and electron microscopic analysis. The amount of interstitial fibrous tissue was determined morphometrically[20] using point counting (5 to 20 test areas per patient, 36 test points per test area) at a magnification of 160:1.

Statistical analyses of the data were performed using *t* test for paired and unpaired analysis when appropriate. Statistical significance was accepted at the $p < 0.05$ level.

Results

Coronary blood flow: Coronary blood flow was 78 ml/100 g·min in control subjects (Group A) and reached the same value of 78 ml/100 g·min in patients with IDC (Group B, Table I) under resting conditions. After administration of dipyridamole, however, in patients in Group B, maximal obtainable coronary blood flow was markedly reduced to 142 ± 38 ml/100 g·min, that is, approximately 50% of the value obtained in Group A with maximal coronary flow rates of 301 ml/100 g·min ($p < 0.001$) (Table I, Fig. 1). Under resting conditions, coronary resistance was 1.03 mm Hg/ml/100 g·min in Group A and 1.04 in Group B (difference not significant [NS]). After dipyridamole administration, coronary

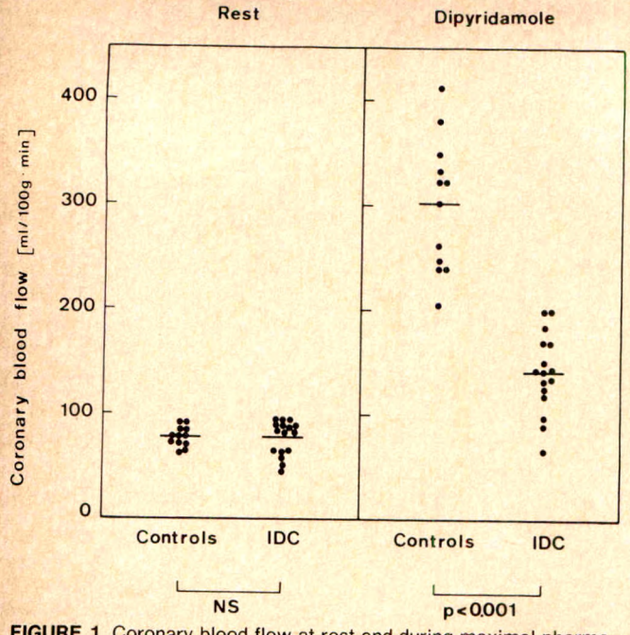

FIGURE 1. Coronary blood flow at rest and during maximal pharmacologically induced coronary vasodilation (dipyridamole 0.5 mg/kg intravenously) in control subjects and in patients with idiopathic dilated cardiomyopathy (IDC). A significant difference in coronary blood flow in control subjects and in patients with IDC was only found after vasodilation with dipyridamole ($p < 0.001$). NS = not significant.

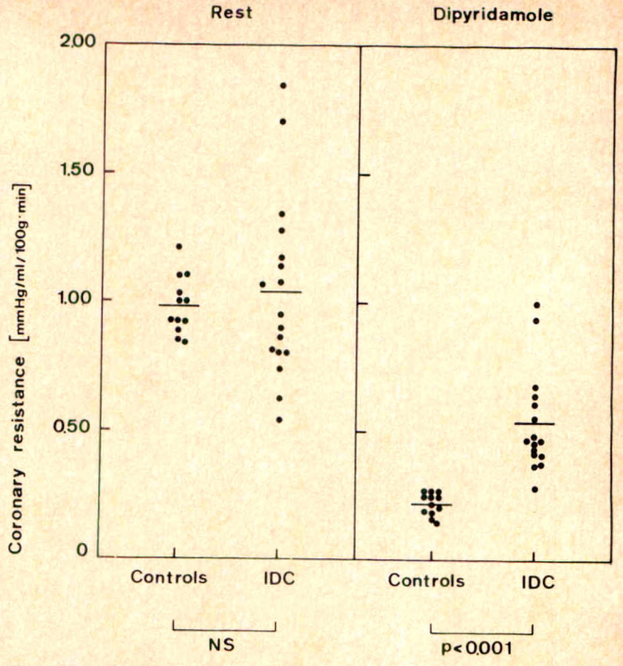

FIGURE 2. Coronary resistance at rest and after application of dipyridamole (0.5 mg/kg intravenously) in control subjects and in patients with idiopathic dilated cardiomyopathy (IDC). A significant difference in coronary resistance in control subjects and in patients with IDC was only found after vasodilation with dipyridamole ($p < 0.001$). NS = not significant.

resistance was reduced to 0.23 mm Hg/ml/100 g·min in Group A, versus 0.54 in Group B; this difference was highly significant ($p < 0.001$) (Table I, Fig. 2). In Group B, mean pulmonary arterial pressure and mean right atrial pressure were significantly elevated under resting conditions ($p < 0.01$ versus control values). After dipyridamole administration, pulmonary arterial pressure and right atrial pressure did not change significantly in either group. Heart rate and systolic and diastolic aortic pressures were comparable in patients in Groups A and B. In Group B, LV end-diastolic pressure was significantly ($p < 0.005$) higher than control values (18.6 mm Hg versus 6.5 mm Hg, Table I).

Coronary and left ventricular angiography: In patients in Groups A and B, coronary arteries and their subbranches were found to be free of even minor luminal irregularities. Data obtained at rest for LV ejection fraction, mean velocity of circumferential fiber shortening, and LV mass are given in Table I. Patients in Group A had a mean LV ejection fraction of 72% (range 68 to 78), compared with 36% (range 18 to 53) in patients in Group B, ($p < 0.001$, Table I). The mean velocity of circumferential fiber shortening in patients in Group B was significantly below the control values (Group A, 1.38 circ/s; Group B, 0.55 circ/s; $p < 0.001$). LV wall thickness was not significantly different in the 2 groups studied: LV mass averaged 73 ± 12.7 g/m^2 in Group A and 122 ± 45.7 in Group B ($p < 0.005$). Regression analysis in patients with IDC indicated that LV end-diastolic pressure ($r = 0.85$) is positively and LV ejection fraction ($r = -0.59$) is negatively related to minimal coronary resistance (Fig. 3 and 4). The 2 regressions are statistically significant ($p < 0.001$, $p < 0.05$). On the other hand, no significant correlation was found between minimal coronary resistance and LV mass ($r = 0.34$, $p > 0.05$).

Left ventricular biopsy: In patients with IDC, light and electron microscopy of specimens taken from LV myocardium (n = 12) showed hypertrophy of the muscle fibers, alterations of the nucleus, and a loss of myofibrils. From each patient, about 10 to 15 arterioles, metarterioles, capillaries, and venules could be analyzed. The arteriolar microvascular segments, ranging in external diameter from 5 to 50 μm, showed no pathologic changes such as intimal proliferation, medial dissection, or mural deposits. The capillary and venular segments also had a normal appearance without thickening of the basal lamina. Volume fraction of the interstitial fibrous tissue was 5.87 ± 5.51 ml/100 ml.

Discussion

Minimal coronary resistance in idiopathic dilated cardiomyopathy: The present study shows almost identical values for coronary blood flow under resting conditions in control subjects and in patients with IDC. A complete separation of the 2 groups, however, could be achieved after pharmacologic vasodilation by application of dipyridamole. Dipyridamole is an almost selective dilator of the coronary artery system[21] which was found to induce maximal coronary vasodilation in control patients at the dosage used in this

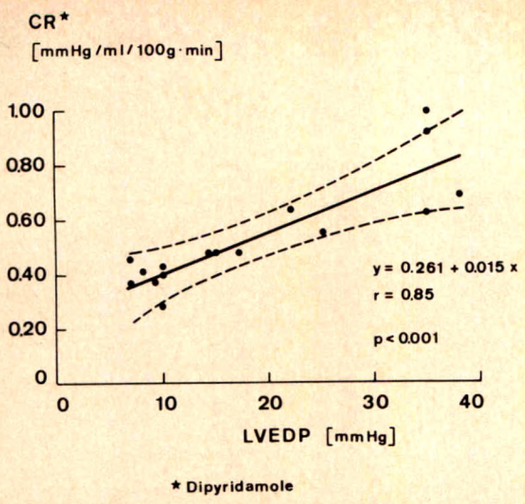

FIGURE 3. Relationship between minimal coronary resistance (CR) after application of dipyridamole (0.5 mg/kg intravenously) and left ventricular end-diastolic pressure (LVEDP) in 16 patients with idiopathic dilated cardiomyopathy. A significant ($p < 0.001$) linear correlation was found. The **dashed lines** represent 95th percentile confidence limits of the regression curve.

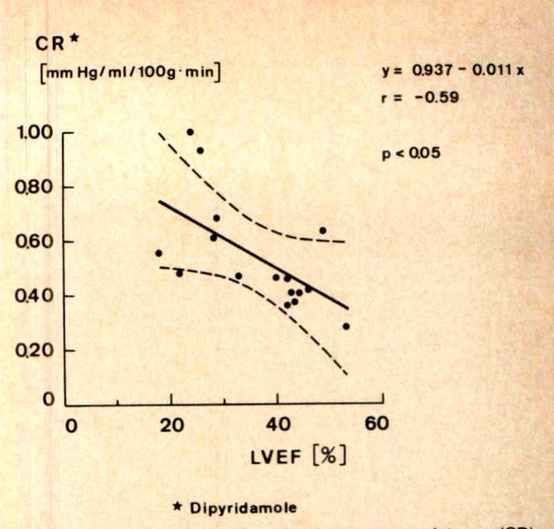

FIGURE 4. Relationship between minimal coronary resistance (CR) and left ventricular ejection fraction (LVEF) in 16 patients with idiopathic dilated cardiomyopathy. A significant ($p < 0.05$) negative linear correlation was found.

study.[9,11,17] Our data confirm that this dosage is sufficient to achieve exhaustion of coronary vascular reserve even in patients with IDC. After application of dipyridamole, minimal coronary resistance could be reduced to 0.23 ± 0.04 mm Hg/ml/100 g·min (range 0.17 to 0.27) in control subjects compared with only 0.54 ± 0.20 (range 0.28 to 1.00) in patients with IDC. The difference between the 2 groups is highly significant ($p < 0.001$) without overlap of the individual values.

Causes of increased minimal coronary resistance in patients with IDC: A similar reduction in coronary dilatory capacity has been observed in patients with coronary heart disease, and has been explained by obstructive lesions of the great epicardial arteries.[9,17] Since in patients with IDC obstructive lesions were not visible in the coronary angiogram, the reduced coronary dilatory capacity could be attributed to 1 of the following mechanisms:

1. The reduction in coronary reserve could be due to abnormalities of small intramyocardial vessels. If this were indeed the case, structural changes would be expected in the specimens taken from LV myocardium. Histopathologic study, however, revealed normal arterioles, metarterioles, capillaries, and venules in the patients studied.

2. A second mechanism that may cause a reduction of coronary reserve in patients with IDC relates to the adaptation of coronary microcirculation to myocardial hypertrophy. Clinical studies[22,23] suggested that increases in minimal coronary resistance do occur in association with LV hypertrophy. Although patients with IDC had an increased LV mass, no significant correlation was found between minimal coronary resistance and LV mass.

3. A third cause of the decreased coronary reserve in patients with IDC could be an increase in the extravascular component of coronary resistance.[14,15,24,25] Studies in animals during maximal coronary vasodilation have demonstrated that extravascular component of coronary resistance is important in the failing heart with increased LV filling pressure.[15] The positive correlation found between minimal coronary resistance and LV end-diastolic pressure confirms that an increased extravascular component of coronary resistance is at least partly responsible for the reduction of coronary dilatory capacity in patients with IDC. In addition, the results obtained in these patients suggest that impaired LV contraction contributes to the reduction in coronary dilatory capacity.

Clinical implications: These findings demonstrate a severe reduction of coronary dilatory capacity in patients with IDC, which may explain the frequent observation of anginal pain during physical exercise. With exertion, LV filling pressure increases, the ejection fraction decreases further, and the end-diastolic volume may increase—all of which will lead to increased intramyocardial extravascular pressure. This might further increase coronary resistance, resulting in myocardial ischemia that may contribute to a deterioration of pump function.

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Prevalence and Significance of an Abnormal S-T Segment Response to Exercise in a Young Athletic Population

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Treadmill stress electrocardiography is employed widely to detect underlying cardiovascular disease in asymptomatic persons. To determine the frequency and significance of an abnormal S-T segment response to exercise in young athletes with increased left ventricular (LV) mass induced by physical conditioning, 75 male isometrically trained athletes without evidence of heart disease (mean age 21 years) and 48 nonathletic young normal subjects were studied by M-mode echocardiography and exercise electrocardiography. Ventricular septal and posterior free wall thicknesses and calculated LV mass were significantly greater in athletes than in control subjects.

An abnormal S-T segment response to exercise was present in 7 (9%) of the 75 athletes, all of whom had a LV mass >275 g and in 5 the LV mass was above the 95th percentile of that of the control subjects. An abnormal treadmill exercise test result also was present in 3 (6%) of 48 control subjects. Seven of the 10 subjects with abnormal exercise test results had radionuclide angiograms at rest and with exercise, each of which was normal. It is concluded, therefore, that (1) abnormal exercise test results occur commonly in both athletes and nonathletes; (2) almost 10% of isometrically trained athletes have "false-positive" exercise electrocardiograms, suggesting that this test has major limitations in screening for underlying cardiovascular disease in athletes; and (3) in athletes, a relation was present between "physiologically" increased LV mass and false-positive exercise test results.

It is well established that chronic athletic conditioning may produce alterations in cardiac structure and function that are usually relatively mild but can mimic certain organic heart diseases.[1,2] In addition, there have been several recent reports of sudden death in athletes,[3,4] causing concern and uncertainty regarding the proper medical evaluation of conditioned athletes.

The exercise (treadmill) electrocardiogram has been employed extensively as a noninvasive screening test to detect underlying cardiovascular disease (particularly coronary artery disease) in asymptomatic persons.[5] However, the frequency and significance of an "abnormal" S-T segment response to exercise in individuals in whom left ventricular (LV) mass was thought to be physiologically increased (that is, induced by athletic conditioning) are unknown. Therefore, to determine the prevalence of positive exercise test results in an athletic population, the relation of such positive tests to "physiologic" left ventricular hypertrophy, and the efficacy of the exercise electrocardiogram in the cardiovascular evaluation of athletes, we performed treadmill exercise studies in 75 young trained athletes, with 48 unconditioned individuals serving as control subjects.

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Methods

The study group consisted of 75 male athletes aged 18 to 39 years (mean 21). Each was engaged in a formal conditioning program which included extensive isometric exercise training (that is, weight lifting). Fifty-nine athletes (40 football players and 19 wrestlers) were participating in intercollegiate athletics at the University of Maryland; the remaining 16 athletes were world-class weight lifters. Each athlete was considered free of organic cardiovascular disease on the basis of medical history and physical examination and the interpretation of the 12-lead electrocardiogram and M-mode echocardiograms. Forty-eight untrained subjects of similar age (range 20 to 57 years, mean 33) without cardiac symptoms or evidence of heart disease served as control subjects.

TABLE I Echocardiographic Findings in 75 Trained Intercollegiate Athletes and 48 Untrained Control Subjects*

	BSA	Wall Thickness VS (mm)	Wall Thickness PW (mm)	LV Mass (g)	$LVID_d$ (mm)
Athletes	2.1 ± 0.2* (1.6–2.6)	11 ± 1 (8–15)	11 ± 1 (8–14)	313 ± 63 (132–429)	55 ± 4 (39–63)
Control subjects	1.9 ± 0.1 (1.5–2.2)	9 ± 1 (8–12)	9 ± 1 (7–11)	205 ± 38 (134–295)	50 ± 3 (43–56)
p value	<0.001	<0.001	<0.001	<0.001	<0.001†

* Data are expressed as mean ± 1 standard deviation; ranges are shown in parentheses.
† When corrected for body surface area, this parameter showed no statistically significant difference between athletes and control subjects.
BSA = body surface area; LV = left ventricular; $LVID_d$ = left ventricular internal dimension in diastole; PW = posterior wall; VS = ventricular septum.

M-mode echocardiography was performed in a standard fashion[6] with a 2.25-MHz, 1.2 cm diameter transducer connected to a Hoffrel 201 ultrasound unit and recorded continuously on light-sensitive paper. Echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography.[7] Estimated LV mass was calculated from the echocardiogram using the method of Troy et al.[8]

A maximal graded treadmill exercise test was performed in all subjects, using a protocol in which the speed was increased 4 mph and the angle of incline increased 2% every 2.5 minutes. A positive S-T segment response to exercise was defined as S-T segment depression ≥1 mm from the J-point, with horizontal or negative slope for a duration of ≥0.08 second, during or immediately after exercise. Radionuclide angiography was performed in 7 subjects at rest and during supine bicycle exercise.[9,10] Before imaging, 10 mCi of technetium-99m–labeled human serum albumin was injected into an antecubital vein. Imaging was accomplished with a conventional Anger camera equipped with a high-sensitivity parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. Statistical analyses were performed using Student's *t* test for nonpaired variables and the chi-square test.

Results

Echocardiographic studies in the athletes showed alterations in cardiac structure consistent with the effects of isometric training[2,11] (Table I, Fig. 1). Ventricular septal and LV posterior free wall thicknesses and calculated LV mass were significantly greater in athletes than in the control subjects, both in absolute terms and when the data were normalized for body surface area. Ratios of ventricular septal to posterior free wall thickness ranged from 0.8 to 1.2 (mean 1.0), and hence no athlete met our criteria for asymmetric septal hypertrophy.[12] Left ventricular transverse diastolic dimension was greater in athletes than in control subjects; however, this difference did not achieve statistical significance when the values were corrected for body surface area. No statistically significant differences were found in the echocardiographic measurements among the 3 different groups of athletes (football players, wrestlers, and weight lifters).

Positive S-T segment response to exercise was present in 7 (9%) of the 75 athletes, 5 of whom had increased LV mass (above the 95th percentile of that of the control subjects). All athletes with positive S-T segment responses had an LV mass >275 g (Fig. 2).

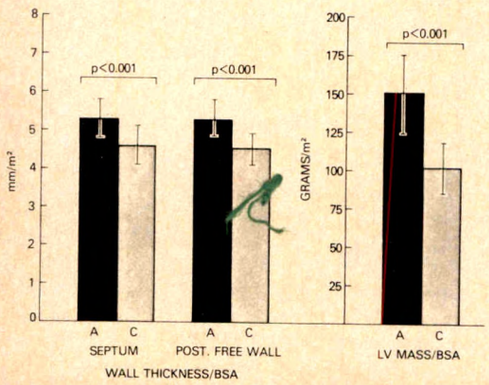

FIGURE 1. Ventricular septum and posterior (POST.) left ventricular free wall thicknesses and left ventricular (LV) mass calculated from the echocardiogram and adjusted for body surface area (BSA). Data are shown separately for athletes (A) and control subjects (C).

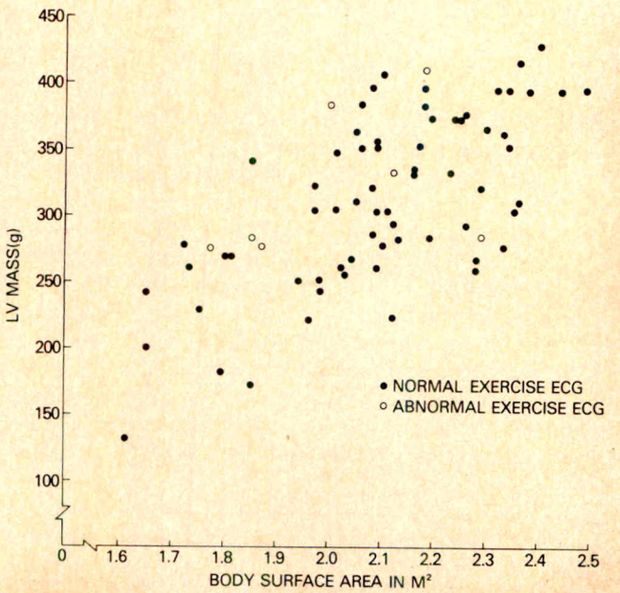

FIGURE 2. Left ventricular (LV) mass calculated from the echocardiogram and related to body surface area in trained athletes. Athletes with abnormal S-T segment responses to exercise are shown by **open symbols**; all others are indicated by **solid symbols.**

TABLE II Echocardiographic Findings in Athletes and Control Subjects With Negative and Positive Exercise Tests*

	Patients (n)	Wall Thickness		LV Mass (g)
		VS (mm)	PW (mm)	
Athletes				
Negative Ex test	68	11 ± 1 (8–15)	11 ± 1 (8–13)	311 ± 64 (132–429)
Positive Ex test	7	11 ± 2 (10–15) p >0.05	11 ± 2 (10–14) p >0.05	321 ± 55 (276–410) p >0.05
Control subjects				
Negative Ex test	45	9 ± 1 (8–12)	9 ± 2 (7–11)	208 ± 36 (134–295)
Positive Ex test	3	9 ± 1 (8–10) p >0.05	9 ± 2 (7–10) p >0.05	162 ± 34 (136–200) p <0.05†

* Data are expressed as mean ± 1 standard deviation; ranges are shown in parentheses.
† When corrected for body surface area, this parameter showed no statistically significant difference between controls with negative and positive exercise test results.
Ex = exercise; LV = left ventricular; PW = posterior left ventricular free wall; VS = ventricular septum.

TABLE III Clinical and Echocardiographic Findings in 7 Athletes With Abnormal Exercise Tests

Athlete	Age (yr)	HR (beats/min) at Onset of S-T Depression	LV Mass		LV Function*
			g	g/m²	
1	17	140	276	156	Not tested
2	19	145	384	214	Normal
3	20	145	333	157	Normal
4	19	160	278	149	Normal
5	21	170	410	188	Normal
6	27	170	285	124	Normal
7	20	190	284	141	Not tested

* Evaluated by gated blood pool scintigraphy at rest and with bicycle exercise.
g/m² = mass (in grams) corrected for body surface area in meters squared; HR = heart rate; LV = left ventricular.

However, when athletes (or control subjects) with positive results on exercise tests were compared to those with normal test results, the groups did not differ significantly with regard to the magnitude of ventricular wall thicknesses and LV mass (Table II).

S-T segment depression appeared at heart rates <150 beats/min in 3 athletes and >150 beats/min in the other 4 (Table III). The 7 athletes with abnormal treadmill electrocardiograms were aged 17 to 27 years (mean 21).

A positive S-T segment response to exercise also was identified in 3 (6%) of the 48 control subjects. The 3 control subjects with abnormal treadmill electrocardiograms were aged 22 to 26 years (mean 24). Although positive exercise test results were more common in athletes than in control subjects, this difference did not achieve statistical significance (p >0.05).

Radionuclide angiography was performed in 7 of the 10 individuals with abnormal treadmill electrocardiograms (5 athletes and 2 control subjects). In each of these subjects the ejection fraction was within normal limits at rest (mean 58%, range 47 to 68) and increased by >5% during bicycle exercise (mean 72%, range 60 to 90). Left ventricular wall motion also was normal at rest and during exercise in each subject. The 2 athletes and 1 control subject with abnormal treadmill electrocardiograms who did not have radionuclide angiographic studies were 17, 20, and 26 years of age, respectively.

Discussion

These data show that young trained athletes without cardiovascular disease but with "physiologic" hypertrophy (that is, increased LV mass induced by chronic conditioning) commonly have an abnormal S-T segment response to treadmill exercise. The prevalence of "false-positive" exercise tests in our athletic population was slightly higher, but did not differ significantly from that in a nonathletic youthful control group. Evidence that these positive exercise tests do represent false-positive results rather than a manifestation of covert coronary artery disease is suggested by the finding that all athletes with abnormal exercise electrocardiograms (who underwent exercise radionuclide studies) demonstrated normal global and regional wall function. Furthermore, each athlete was young (≤30 years) and asymptomatic, making the possibility of coronary artery disease quite unlikely.

This study suggests that the increased LV mass induced by physical training might be partly responsible for the "ischemic" electrocardiographic changes seen with exercise. Each "abnormal" exercise test result in

the athletes occurred in subjects with LV mass >275 g; furthermore, in 5 of the 7 athletes with an abnormal exercise response the LV mass was above the 95th percentile of that of the control population. However, the relation between estimated LV mass and positive S-T segment response to exercise that we identified cannot be considered definitive. Mean LV mass in athletes with a positive S-T segment response to exercise was greater, but not significantly different from the LV mass in athletes with normal exercise test results. Also, we found no relation between calculated LV mass and abnormal S-T segment response to exercise in the control group.

Recently, investigators have emphasized that asymptomatic and healthy appearing competitive or recreational athletes may die of undetected and unsuspected cardiovascular disease.[3,4] Although a variety of cardiac structural malformations may be responsible for these deaths, hypertrophic cardiomyopathy is most common in young athletes and coronary artery disease is most common in older persons. However, the most efficient and reliable method for screening athletes for occult cardiovascular disease before participation in sports has not been established. This problem is important, affecting enormous numbers of vigorous and otherwise healthy young men competing in athletic programs. Our finding that a substantial proportion (almost 10%) of primarily isometrically trained athletes have false-positive results on exercise electrocardiograms suggests that the exercise stress electrocardiogram has major limitations as a reliable screening test for underlying cardiovascular disease in young athletes.

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Heterogeneity of Left Ventricular Segmental Wall Thickening and Excursion in 2-Dimensional Echocardiograms of Normal Human Subjects

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Regional abnormalities of left ventricular (LV) wall thickening and excursion have been demonstrated by 2-dimensional (2-D) echocardiography. However, the variability of normal segmental contraction has not previously been defined. We performed 2-D echocardiography in 12 normal men aged 19 to 27 years. We obtained short-axis images at the level of the mitral valve, chordae tendineae, papillary muscles, and apex at end-diastole and end-systole. A computer-based system divided each short-axis image into 12 cavity and wall segments, and analyzed percent systolic wall thickening along each radius and percent area change of each cavity segment. Overall variability of contraction as well as the contributions of several sources of variability were determined. The overall range of cavity segment area change was 0 to 100% and of segmental wall thickening was 0 to 150% in these normal subjects. Average contraction was similar at different ventricular levels. Significant differences were found between adjacent segments at each level as well as between subjects. Intrathoracic cardiac rotation and motion were minimal; correction for these movements did not significantly alter the variability of contraction as calculated from 2-D echocardiograms. Temporal asynergy of contraction did contribute to variability; correction resulted in a significant alteration in mean segmental area change (from 59 ± 20% [standard deviation] uncorrected to 66 ± 16% corrected, $p < 0.001$) and in mean segmental wall thickening (58 ± 29% uncorrected to 71 ± 34% corrected, $p < 0.01$). Substantial interexamination variability also occurred with an average difference in cavity segment area change of 20% per segment and in segmental wall thickening of 29% per segment between 2 analyses by the same observer. Thus, considerable intersegmental and intersubject variability of LV contraction occurs in normal subjects as exhibited on 2-D echocardiograms, exaggerated by technical difficulties in analyzing and reproducing the echocardiographic tracings. Significant differences in segmental wall thickening and endocardial excursion may occur in adjacent segments in normal subjects, and therefore such differences alone may not indicate cardiac disease.

Two-dimensional (2-D) echocardiography is well suited to the study of regional left ventricular (LV) contraction because of its ability to detect and depict wall excursion and thickening in real time.[1] Regional LV function is commonly evaluated by inspection of real-time echocardiographic images to qualitatively assess the symmetry of LV contraction. Regional asymmetry of LV wall motion and thickening is generally taken to indicate myocardial ischemia or infarction, or both.[2–5] This approach requires the assumption that symmetric wall motion is characteristic of normal LV function and that segmental variation or hypokinesia is a specific sign of ischemic heart disease. However, experimental and clinical studies have defined important regional differences in normal myocardial contraction.[6–14] Recent evidence suggests that LV contraction may exhibit considerable regional variability in 2-D echocardiograms.[12,13] The extent of this variability in 2-D echocardiograms in normal subjects must be defined to use the echocardiographic technique in accurately identifying and diagnosing segmental ventricular dysfunction.

Our hypothesis was that regional variability in LV wall excursion and thickening would be found in 2-D echocardiograms and that this variability would be due

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to both biologic and technical factors. It was the goal of this study to (1) define the range of regional LV wall thickening and excursion in normal human subjects at rest, studied by standard 2-D echocardiographic techniques, and (2) explore some technical and physiologic factors contributing to regional variability of contraction on echocardiograms.

Methods

Subjects: Twelve men aged 19 to 27 years comprised the study population. No subject gave a history of cardiac disease or symptoms. All had a normal physical examination and M-mode echocardiogram. All subjects were in normal sinus rhythm without electrocardiographic conduction abnormalities. An additional criterion for inclusion in the study was our ability to obtain excellent quality 2-D echocardiographic images in each subject.

Echocardiographic recording: Two-dimensional echocardiograms were obtained using a Toshiba SSH-10A Sonolayergraph, with an electronically phased array transducer operating at 2.4 MHz. Studies were performed with the patient in the left lateral decubitus position, using standard techniques.[1] Short-axis parasternal images were obtained at the level of the mitral valve leaflets, chordae tendineae, papillary muscles, and apex (that is, below the papillary muscles). Echocardiograms were recorded on videotape for subsequent analysis.

Analysis of Echocardiograms

1. Echocardiograms recorded on videotape were reviewed in realtime and in slow motion. Our initial time references for stop-frame analysis were *end-diastole*, defined as the peak of the electrocardiographic R wave and *end-systole*, defined as the minimum apparent cross-sectional cavity area. The end-diastolic and end-systolic epicardial and endocardial boundaries, and centimeter calibration marks, were traced from stop-frames using transparent plastic sheets placed over the video monitor. For consistency, we traced the inner borders of the endocardium and epicardium. When tracing the borders on the papillary muscle level images, the outlines of the papillary muscles themselves were excluded from the contour.

2. The epicardial and endocardial boundaries and calibration marks were digitized using a Talos digitizing tablet, interfaced to a PDP 11/34 computer and to a Ramtek image display system. This method was interactive and allowed the investigators to immediately view the digitized contours and retrace if necessary.

3. A landmark in each image was the posterior junction between the endocardium of the right ventricular free wall and the right ventricular septal endocardium. We defined the ventricular diameter as the longest line (determined by the computer) from this landmark to the LV anterolateral wall epicardium; this divided the ventricle approximately in half (Fig. 1). The midpoint of this diameter was used as the center of the short-axis image. From this center, 12 radii at 30° intervals were generated, dividing the short-axis image into 12 approximately equal LV cavity and LV wall segments. Segments 1 to 4 correspond approximately to the ventricular septum, 5 to 8 to the anterolateral, and 9 to 12 to the posterior LV wall.

4. For each short-axis image, systolic thickening of each wall segment along each radius and systolic decrease in each LV cavity segment area were calculated and expressed as percent change from end-diastole. Our algorithms for these measurements were all tested on tracings of various geometric shapes to validate their accuracy.

5. The average percent cavity segment area change and percent wall thickening were calculated for *all* segments and radii studied, and standard deviations computed.

6. The range of cavity segment area change or wall thickening *per subject* was noted (that is, the difference between the highest and lowest cavity segment area change and percent wall thickening at each ventricular level in each individual subject).

Analysis for Sources of Variability

1. *To determine whether the pattern of contraction varied systematically at different levels of the ventricle*, the average cavity segment area change and wall thickening at individual ventricular levels were calculated for all subjects. The specific levels chosen were mitral, chordal, and papillary muscle levels. Mean values and standard deviations were calculated and the significance of differences between levels assessed by analysis of variance.

2. *To determine whether the heterogeneity of contraction varied systematically in different segments at a given level of the ventricle*, the average percent ventricular cavity segment area change and percent wall thickening were calculated for each of the 12 myocardial segments at each level for all subjects; standard deviations were calculated. The significance of differences found was tested using analysis of variance. To further assess segment-to-segment variability, the relation between contraction of pairs of adjacent segments at each ventricular level was assessed. That is, the contraction of segment 1 was compared with that of segment 2, segment 2 with 3, segment 3 with 4, and so forth, including segment 12 compared with segment 1 (Fig. 1). A correlation coefficient was calculated for each of these segment pairs, in all subjects, at mitral, chordal, and papillary muscle levels, for both segmental wall thickening and cavity segment area change.

3. *To determine the effect of cardiac rotation and translational motion*, end-systolic and end-diastolic images were entered into the image-processing system. The diameter and center of the end-systolic images were determined in the same way as that used for the end-diastolic images. The amount of

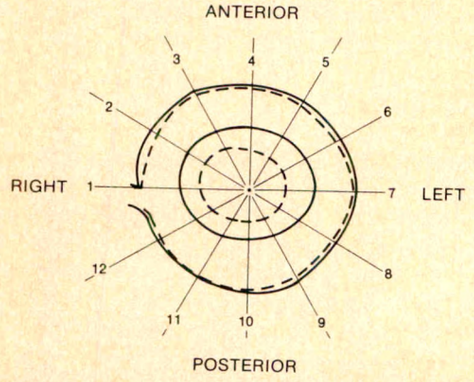

FIGURE 1. Method used for analysis of regional left ventricular contraction in a schematic of a short-axis 2-dimensional echocardiographic image. The junction between the posterior right ventricular free wall endocardium and right ventricular septal endocardium was chosen as a landmark, and a line drawn to the farthest point on the lateral left ventricular wall epicardium. This line (line 1-7) was designated as a cavity diameter and bisected to identify the cavity center. Twelve equidistant radii were drawn to separate the image into 12 cavity and wall segments. Percent area change of each cavity segment and percent thickening of the wall along each radius during systole were calculated. **Solid lines** represent end-diastole, and **interrupted lines** end-systole.

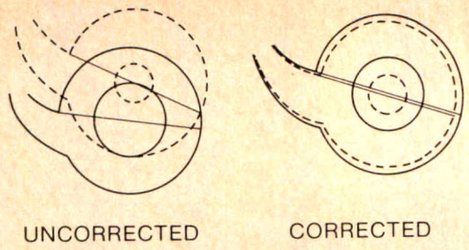

FIGURE 2. Correction for cardiac rotation and motion. The previously determined left ventricular landmark and diameter were used to realign the systolic onto the diastolic image. **Left,** schematic end-diastolic (**solid lines**) and end-systolic (**interrupted lines**) short-axis 2-dimensional echocardiographic endocardial and epicardial borders before correction. **Right,** the 2-dimensional echocardiographic borders after realignment.

systolic rotation of the LV diameter about the cavity center (in degrees) and the intrathoracic motion of the center and diameter (in mm) between end-diastole and end-systole were calculated. The center and diameter of the end-systolic image were then realigned onto those of the end-diastolic image. Data were analyzed both with and without this realignment (Fig. 2). That is, the overall values for wall segment thickening and cavity segment area change were calculated for the images with and without realignment to assess the effect of "correcting" the images for cardiac rotation and translation during contraction. The significance of differences found in left ventricular contraction indexes derived by the 2 methods was assessed by analysis of variance.

4. *To assess the contribution of temporal asynergy of contraction to variability*, end-diastolic outlines were traced at the peak of the electrocardiographic R wave, and end-systolic frames were initially traced at an arbitrary point of apparent minimum cavity area, as described earlier. To delineate the pattern of contraction at other points in the cardiac cycle, additional images were traced 33 ms (1 videotape frame) and 66 ms (2 frames) before and after the previously determined "end-systolic" frame. The average cavity segment area change and wall thickening were calculated using the *maximum percent cavity segment area change* and *maximum segmental wall thickening* found for each segment at any point in the cardiac cycle, no matter which of the 5 "end-systolic" frames showed this maximum contraction of a particular segment. This analysis was carried out in 5 of our subjects, using chordal level images. Differences between left ventricular contraction indexes calculated by the 2 methods (the "maximum contraction" method versus our earlier method using a single "end-systole"), that is, methods with and without correction for temporal asynergy, were assessed by analysis of variance.

5. *To assess the effects of interexamination variability*, the same observer, using the original videotape, traced end-diastolic and end-systolic outlines at chordal level on 2 different occasions, 6 months apart, for each of 5 of our subjects. The observer attempted to identify the same ventricular level and the same points in the cardiac cycle, but was not necessarily tracing from the same frame on both occasions. The initial, single "end-systolic" method was used for this portion of the study. The average differences between segmental area change and segmental thickening, as determined on the 2 occasions, as well as the range of differences per segment were calculated.

Results

Four hundred fifty-six ventricular cavity and wall segments were analyzed: (1) 12 segments at each of 2 levels (chordal and papillary muscle) for each of the 12 subjects (288 segments); (2) 12 segments at mitral level for each of 11 subjects (1 subject yielding technically inadequate mitral level images) (132 segments); and (3) 12 segments at apical level for each of 3 subjects (36 segments). In the other 9 subjects, apical level images of adequate technical quality were not obtained.

Overall data: Figure 3 shows, in graphic form, our data for cavity segment area change and wall thickening for all segments at all levels of all subjects. The average segment area change was 54.4% with a range of 0 to

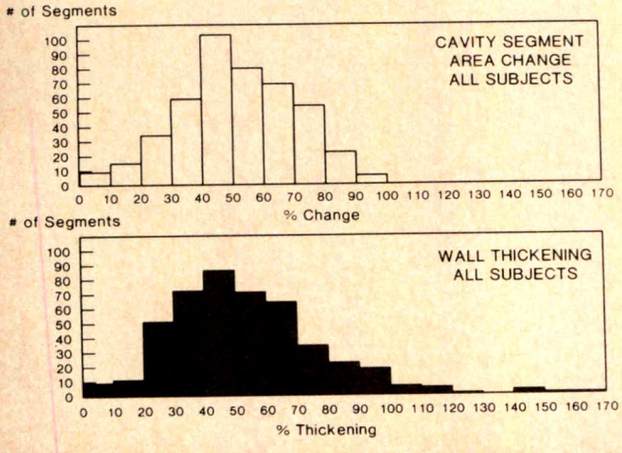

FIGURE 3. Overall distributions of cavity segment area change and wall thickening in all subjects studied, at all levels (456 segments). **Above,** percent cavity segment area change. **Below,** percent segmental wall thickening.

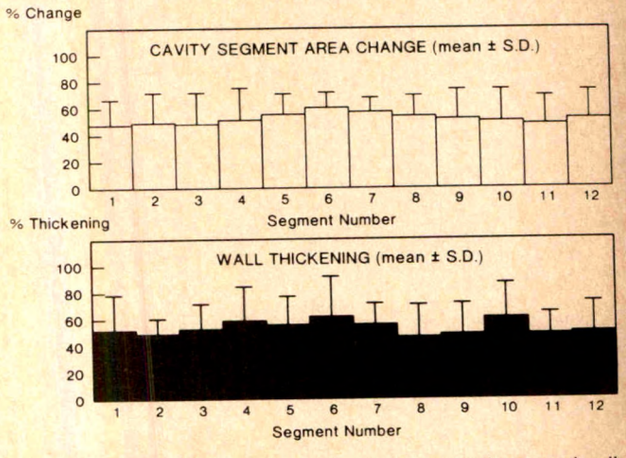

FIGURE 4. Regional variation in cavity segment area change and wall thickening. These data show left ventricular contraction indexes in all subjects at papillary muscle level. **Above,** cavity segment area change for each of the 12 segments at papillary muscle level. **Below,** percent wall thickening along each of the 12 radii at papillary muscle level. No significant differences in mean segmental contraction were found. S.D. = standard deviation.

TABLE I Intersubject Variability of Left Ventricular Contraction at Different Ventricular Levels*

Subject	Percent Cavity Segment Area Change Levels			Percent Wall Segment Thickening Levels		
	Mitral	Chordal	Papillary Muscle	Mitral	Chordal	Papillary Muscle
1	†	54 (16–87)	51 (20–75)	†	68 (43–97)	56 (29–97)
2	23 (5–46)	35 (15–48)	44 (16–59)	66 (27–143)	51 (26–80)	71 (29–102)
3	50 (40–56)	43 (34–52)	65 (55–80)	65 (27–97)	51 (27–102)	62 (33–89)
4	36 (17–50)	59 (43–77)	63 (36–84)	34 (4–79)	56 (29–102)	88 (40–169)
5	30 (13–54)	48 (31–57)	54 (41–72)	39 (27–60)	39 (19–64)	52 (16–87)
6	34 (−5–70)	47 (20–65)	31 (10–54)	62 (17–120)	71 (33–97)	39 (15–65)
7	61 (40–75)	66 (50–82)	66 (42–82)	46 (9–73)	47 (13–83)	47 (27–97)
8	50 (36–66)	55 (29–77)	57 (40–77)	35 (21–53)	39 (2–66)	30 (8–46)
9	46 (21–64)	56 (34–79)	42 (25–59)	37 (18–51)	46 (3–94)	46 (21–72)
10	55 (32–70)	50 (43–58)	54 (39–65)	57 (33–121)	73 (47–95)	46 (24–77)
11	45 (34–61)	29 (0–68)	38 (19–55)	62 (49–82)	29 (−4–41)	40 (21–64)
12	59 (42–69)	50 (0–85)	68 (46–91)	67 (7–157)	61 (31–117)	54 (30–100)
Overall average ± SD	44 ± 17	49 ± 19	53 ± 18	52 ± 27	53 ± 23	53 ± 24

* Values for each subject include the mean contraction of the 12 segments at a given level, followed by the range of contraction at that level (that is, lowest-to-highest segmental contraction).
† Technically inadequate for evaluation.
SD = standard deviation.

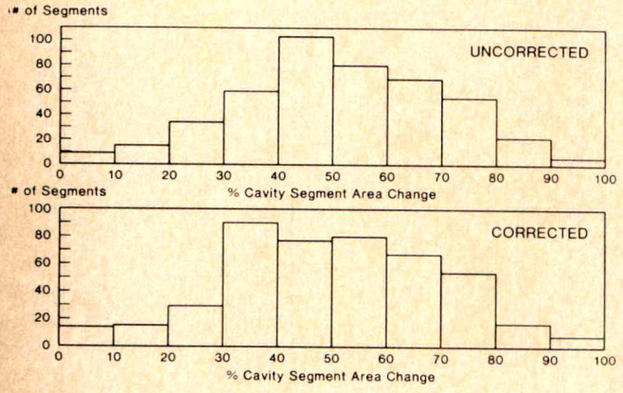

FIGURE 5. Cavity segment area change before and after correction for cardiac rotation and motion. No significant changes were found in mean contraction or in the range of contraction after realignment of the systolic and diastolic images.

100%. The average segmental wall thickening was 54.0% with a range of 0 to 150%. Systolic thinning was observed in 1 of 456 segments and systolic increase in cavity segment area was observed in 3 of 456 segments (<1% in each case). We presumed this systolic thinning and cavity expansion to be artifactual in these normal subjects, possibly due to either echocardiographic dropout or inaccuracies in tracing, or both; these segments were excluded from further analysis.

No consistent differences in average contraction of the major ventricular regions were found. That is, segments of the ventricular septum, anterolateral wall, and posterior wall did not exhibit differences in mean cavity segment area change or mean segmental wall thickening (Fig. 4). Similarly, no significant differences in average contraction were found among the 3 ventricular levels studied (that is, mitral, chordal, and papillary muscle) (Table I). The apical level results were not compared

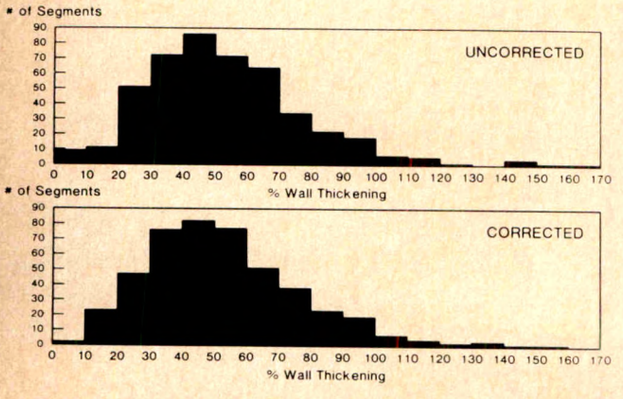

FIGURE 6. Wall segment thickening before and after correction for cardiac rotation and motion. Mean contraction and the range of contraction did not change after realignment of images.

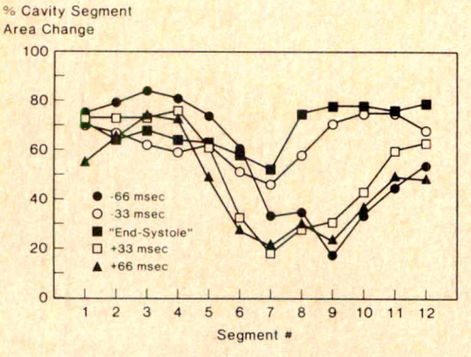

FIGURE 7. Temporal asynergy of cavity segment area change in 1 subject. The cavity segment area change for each of the 12 segments is plotted separately for each of 5 points around end-systole: 66 ms before end-systole, 33 ms before end-systole, end-systole, 33 ms after end-systole, and 66 ms after end-systole. Segments of the ventricular septum (1 to 4) reach peak contraction before other ventricular regions.

with those at the other levels, because of the small number of segments that could be analyzed. However, the data in Table I show the significant subject-to-subject differences that were found in both mean cavity segment area change ($p = 0.0001$) and mean segmental wall thickening ($p = 0.00001$).

The analysis of correlations between thickening of adjacent pairs of segments revealed a range of correlation coefficients from $r = 0.14$ to $r = 0.86$ with an average of $r = 0.58 \pm 0.18$. For area change of adjacent pairs of cavity segments, correlation coefficients ranged from $r = 0.54$ to $r = 0.95$ with an average of $r = 0.85 \pm 0.09$. The correlation coefficients indicate the degree of segment-to-segment variability in our data, more marked for segment thickening than for cavity segment area change. This intersegment variability of contraction is also demonstrated by the wide range of contraction noted in individual levels in each subject (Table I).

Intrathoracic cardiac rotation and motion: The average systolic cardiac rotation was $1.0 \pm 7.6°$ counterclockwise. The average systolic intrathoracic translational motion was 1.7 ± 21.4 mm to the right and 6.7 ± 37 mm anteriorly. We did not find a consistent direction of rotation, some subjects exhibiting clockwise and some counterclockwise rotation during systole. Similar subject-to-subject variability was found in the anteroposterior and right-left motion vectors.

Correction for intrathoracic systolic rotation and motion (that is, realignment of end-systolic and end-diastolic centers and diameters) did not significantly alter the mean values for segment area change or wall thickening nor the wide range of contraction (Fig. 5 and 6).

Temporal asynergy of contraction: Substantial temporal variability of the pattern of contraction was found for both cavity segment area change and wall thickening. That is, different segments of the ventricle reached peak contraction at different points in the cardiac cycle, and the pattern varied from subject-to-subject. For example, in some subjects, segments of the ventricular septum reached their peak cavity segment area change or peak wall thickening earlier than did segments of the anterolateral or posterior wall (Fig. 7). In other subjects, the pattern was reversed or other patterns were noted.

The degree of variability (that is, the range) of left ventricular cavity segment area change decreased somewhat after "correction" for temporal asynergy. Using the maximum cavity area change for each segment at any point in the cardiac cycle (of the 5 points studied near "end-systole") yielded a narrower distribution of this contraction index (Fig. 8). This narrowing of the distribution was due to relatively fewer low values for segment area change. This change in distribution caused a significant increase in mean segmental area change (from $58.8 \pm 19.6\%$ to $66.2 \pm 16.4\%$, $p < 0.001$). A significant increase in mean segmental thickening (from $58.1 \pm 29.4\%$ to $71.1 \pm 34.2\%$, $p < 0.01$) was also found, but the range of segment thickening remained wide (Fig. 9).

Interexamination variability: The average difference in cavity segment area change between the 2 tracing sessions was 20.4% with differences per segment ranging from 0 to 85%. The average difference in segmental wall thickening was 29.4%, with differences per segment ranging from 0 to 103%.

Discussion

The major finding of our investigation was that normal human LV contraction, as depicted in 2-D echocardiograms, is characterized by substantial intersegmental and intersubject heterogeneity. How do our results compare with those of other investigators who have studied the pattern of LV contraction using ultrasound as well as other imaging techniques? What biologic and technical factors may have contributed to the variability found in the present study?

Previous studies of regional LV contraction: The contraction patterns of human and canine left ventricles have been studied extensively by several techniques, including single and biplane contrast ventriculography,[11,14–16] cinefluorography,[17] coronary cineangiography,[8] biplane videometry,[18] implanted radioopaque markers,[14,19] implanted sonomicrometers,[9,20] radio-

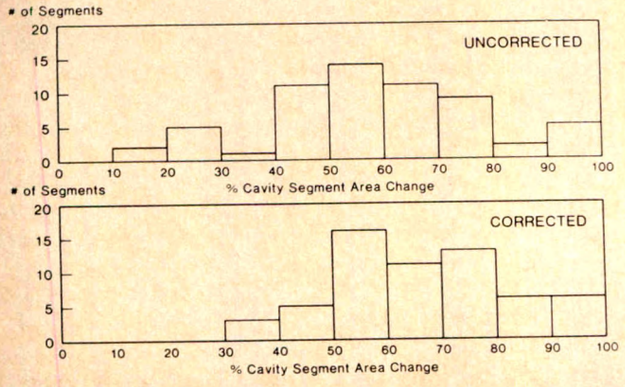

FIGURE 8. Cavity segment area change before and after correction for temporal asynergy. Average contraction increased significantly after correction for asynergy.

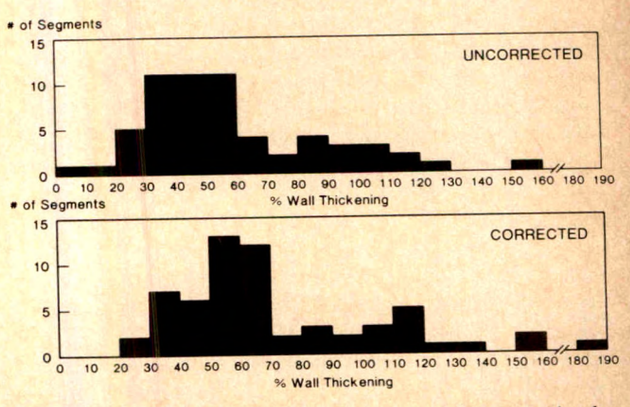

FIGURE 9. Wall segment thickening before and after correction for temporal asynergy. Average contraction increased significantly after this correction.

isotope ventriculography,[21] and echocardiography.[10,12,13,22,23] The general consensus is that LV ejection is accomplished by symmetric contraction of the ventricle, chiefly by circumferential fiber shortening.[24] However, regional differences in wall excursion have previously been demonstrated, with the LV free wall having a larger excursion than the ventricular septum.[8,25] Similarly, LeWinter et al,[9] using implanted sonomicrometers in dogs, showed an increase in shortening of hoop-oriented fibers at the ventricular apex compared with the mid-LV level. In these previous studies, information was gathered largely using techniques capable of evaluating only a limited portion of the LV cavity, and usually measuring endocardial excursion and not regional wall thickening. Discrepancies were found between regional endocardial excursion as displayed on contrast angiographic versus implanted marker studies, possibly due to the effects of infolding of endocardium in the contrast angiographic studies.[17]

Echocardiography is uniquely suited to the study of LV contraction, because of the ability to display both endocardial excursion and wall thickening of a portion of the left ventricle in real time. Initially, M-mode echocardiography was used to establish relatively narrow normal ranges of LV contraction, with excursion and thickening of the posterior wall being larger than those of the ventricular septum.[1] Recent 2-dimensional echocardiographic studies of regional LV contraction revealed a regional variability more substantial than that suggested by studies using other techniques.[12,13] Franklin et al[12] measured the motion of endocardium at radial separations of 10° around the short-axis circumference in 2-D echocardiograms, and found a 5-fold variation in maximum movement of individual endocardial targets toward a mean centroid. Greater than 25% variation was found in regional wall thickening along individual radii. Folland et al[13] observed more modest variability in a 2-D echocardiographic evaluation of endocardial motion. They found that a cavity segment area analysis technique (as an analog of endocardial excursion) revealed less variability than did measuring endocardial motion along a radius. Finally, Likoff et al,[26] using an echocardiographic crystal placed on the epicardium of open-chest human subjects, revealed marked heterogeneity of myocardial function in areas without known infarction or abnormality on angiogram. Thus, regional variability of contraction appears to be a feature of normal left ventricles.

Factors contributing to variability of ventricular contraction seen in 2-D echocardiograms: Several factors may have contributed to the contractile variability demonstrated in our study. Not all of these factors are unique to echocardiography; they influence other imaging techniques as well.[27] A summary of factors contributing to variability in our study is found in Table II.

Biologic contributors to variability may include regional differences in myocardial perfusion, previously demonstrated by Falsetti et al,[28] and variable LV fiber architecture.[29] In addition, temporal asynergy of contraction is an important factor to consider. All normal

TABLE II Factors Contributing to Regional Variability in Left Ventricular Contraction on 2-Dimensional Echocardiograms

I. Biologic factors
   A. Regional myocardial perfusion
   B. Variable muscle fiber architecture
   C. Temporal asynergy of contraction
II. Technical factors
   A. Frame of reference (correction for cardiac rotation and motion)
   B. Identification of endocardium and epicardium
   C. Gain dependence of image appearance

LV segments do not reach peak contraction simultaneously.[30] Therefore, any technique that arbitrarily evaluates LV wall motion at only 2 points in the cardiac cycle (end-diastole and end-systole) might show artifactual regional differences in contraction. In the present study, temporal asynergy of contraction was a modest contributor to the regional variability we found. When we used the *maximum* contraction of each segment, no matter when in the cardiac cycle it occurred, the overall heterogeneity of segmental area change decreased. Therefore, accurate characterization of regional LV function will require the evaluation of several points in the cardiac cycle.

Several important technical limitations of 2-D echocardiography may have contributed to the variability found in this study. The presence of intrathoracic cardiac rotation and motion was confirmed in our study, but the absolute amount of motion was small. Furthermore, when we corrected for this motion, significant regional variability was still apparent. This finding confirms previous work by Moynihan et al[23] who found that the use of a fixed or "floating" frame of reference made little difference in the analysis of regional left ventricular function.[23]

An important prerequisite for accurately depicting regional wall motion and thickening using echocardiography is the accurate definition of endocardial and epicardial boundaries. Some recent evidence suggests that definition of the endocardium may be difficult on 2-D echocardiograms.[31] Furthermore, measurements of cavity dimensions and wall thickness taken from 2-D echocardiograms may be less reproducible than M-mode measurements, and may correlate poorly with those obtained using M-mode techniques.[32,33] These problems stem in part from several technical limitations of image generation in current 2-D ultrasound systems, such as the dependence of structure appearance on gain or amplification settings.[34]

One manifestation of indistinct target identification in the present study may be the large interexamination variability we found. In our study, we did not examine interexamination or interobserver variability in tracing borders from the same frame. Instead, we attempted to evaluate the variability inherent in measuring regional cardiac contraction on 2 occasions from the same study, attempting to identify comparable frames at the same ventricular level. We believe that this type of interexamination variability has clinical relevance specifically for following up patients with serial echocardiographic

examinations. Parallax may have been an additional problem in our tracings, and newer image analyzers may decrease variability, because some of these systems superimpose a marker or cursor directly on the video image during tracing. The observer in our study may also have had difficulty in identifying the same ventricular level on 2 successive viewings of the videotape. Precise, reproducible landmarks may be difficult to locate in the closed-chest subject, and the patient's position and the transducer orientation may vary between examinations and during an examination. These factors may decrease reproducibility.

The variability demonstrated in the present study precludes the use of simple, qualitative assessment of the symmetry of contraction as a method of identifying segmental ventricular dysfunction. The wide range of normal contraction makes it difficult to identify the contraction of a given segment as abnormally decreased based simply on a comparison with the contraction of adjacent segments. Thus, echocardiographic "hypokinesia" is nonspecific and may be a normal variant that does not necessarily indicate segmental ventricular dysfunction. However, because our study, as well as those of others,[3,35] indicate that wall thinning and dyskinesia are rare findings in normal subjects, these abnormalities may be reliable indicators of abnormal regional LV contraction.

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Cardiac Function in Sickle Cell Anemia

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Although ventricular dysfunction is suspected to underlie congestive heart failure in sickle cell anemia (SCA), ejection indexes of left ventricular (LV) pump performance have been found to be normal. The increased preload and decreased afterload of SCA increases the ejection phase indexes and might obscure true LV dysfunction. Therefore, the preload and afterload independent end-systolic stress-volume index was compared in 11 patients with SCA and in 11 normal volunteers. End-systolic pressure and echocardiographic LV dimensions were determined during rest, leg raise, hand-grip and amyl nitrite inhalation. Systemic vascular resistance (afterload) was decreased to 1,033 ± 314 dynes s cm^{-5} (mean ± standard deviation) in SCA from 1,701 ± 314 dynes s cm^{-5} in normal subjects. End-diastolic volume index (preload) was increased to 102 ± 24 ml/m^2 in SCA from 66 ± 10 ml/m^2 in normal subjects. Cardiac index was increased to 4.7 ± 1.1 liters/min/m^2 in SCA from 2.8 ± 0.8 liters/min/m^2 in normal subjects. Ejection fractions were similar: 0.59 ± 0.09 in SCA versus 0.62 ± 0.07 in normal subjects. However, in patients with SCA, the ratio of resting end-systolic stress-volume index was decreased (1.5 ± 0.5 in SCA versus 2.8 ± 0.6 in normal subjects) and the slope of the end-systolic stress versus end-systolic volume index relation was decreased (2.7 ± 1.3 in SCA versus 4.4 ± 1.8 in normal subjects), suggesting LV dysfunction in those patients. Thus, LV muscle contractile performance is depressed in SCA. Increased preload and decreased afterload compensate for the LV dysfunction and maintain a normal ejection fraction and high cardiac output.

Symptoms of congestive heart failure are frequent in patients with sickle cell anemia (SCA),[1–3] raising the possibility of depressed cardiac muscle function.[4] Previous studies suggest that the heart is normal in SCA.[5,6] However, these studies, measured myocardial function by ejection phase indexes that may not detect abnormalities of myocardial function under altered loading conditions.[7] Both preload and afterload are altered in SCA. In severe anemia, cardiac output and stroke volume increase because of both cardiac dilatation and decreased peripheral vascular resistance.[8,9] Cardiac dilatation increases preload and decreased peripheral resistance reduces afterload. Increased preload and decreased afterload result in increased ejection phase indexes, possibly obscuring abnormalities of cardiac muscle function.[7]

To study cardiac muscle function in SCA, indexes of myocardial performance that are independent of loading conditions must be used. The relation between pressure and volume at end-systole is an index of myocardial performance independent of preload and a linear function of afterload.[10–13] This index can be obtained reliably by echocardiography and external pressure recordings.[14] We used the end-systolic stress-volume relation to measure myocardial performance in patients with SCA.

Methods

Patient groups: There were 11 normal volunteers matched for age and 11 patients with SCA. These 2 groups were further subdivided by age, that is, 7 normal adults (aged 28 ± 7 years) were compared with 6 adult patients with SCA (aged 31 ± 7 years). Four normal children (10 ± 4 years) were compared with 5 children with SCA (aged 12 ± 4 years). Patients with SCA were typical clinically and homozygous for hemoglobin-S. SCA was severe in all patients, the hemoglobin averaging 7.9 g/100 ml; all patients had cardiac enlargement on chest roentgenograms, and 3 adults had a history of congestive heart

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failure. No child with SCA had symptoms of congestive heart failure. No patient was studied during sickle cell crisis. Patients with renal failure, systemic hypertension, cor pulmonale, valvular heart disease, clinical, electrocardiographic, or echocardiographic evidence of pericardial disease, or diabetes were excluded. No history or electrocardiographic evidence of angina or myocardial infarction and no M-mode or 2-dimensional (2-D) echocardiographic evidence of regional wall disease was present.

Procedures and methods of study: Echocardiographic studies in adults were performed with a phased array (Varian 3000) echocardiogram machine and a 2.25 MHz transducer. Echocardiographic studies in children were performed with a mechanical sector scan (ATL) echocardiogram machine with a 3.5 MHz transducer. Two-dimensional echocardiography was performed in each individual at rest to exclude regional wall disease. M-mode echocardiograms were performed with the M-mode cursor angled through the center of the left ventricular (LV) cavity just below the mitral leaflets. Blood pressure was recorded from the arm by sphygmomanometer. After resting measurements, simultaneous M-mode echocardiography and blood pressure measurements were performed during supine leg raising, after submaximal hand-grip exercise and immediately after amyl nitrite inhalation. Left ventricular end-systolic and end-diastolic dimensions and end-diastolic posterior wall thickness were measured. End-systolic measurement was taken at the point of maximal excursion of the ventricular septum. End-diastolic dimension was measured at the R wave of the electrocardiogram. Posterior end-diastolic wall thickness was measured from leading edge to leading edge in the standard fashion.[15]

End-systolic pressure was determined from sphygmomanometric measurements of systolic pressure by use of a regression equation. The regression equation was derived from 29 normal patients at cardiac catheterization; end-systolic pressure derived from the intraarterial recording was compared with simultaneously obtained peak-systolic pressure by sphygmomanometer. Dicrotic notch pressures were taken as end-systolic pressures. The equation used was: $Y = 0.66x + 13.55$, where x is the peak systolic pressure by cuff and Y is the calculated end-systolic pressure. The correlation coefficient was 0.88. Ventricular volumes were calculated by the formula of Teicholtz et al.[16] Volumes were converted to volume index by dividing by body surface area. Cardiac output was determined by multiplying echocardiographic stroke volume by heart rate. Systemic vascular resistance was calculated by dividing mean blood pressure by cardiac output. Mean blood pressure was calculated by the following equation: Mean pressure = [systolic pressure + 2 (diastolic pressure)] 3.

Left ventricular end-systolic wall thickness was determined by a modification of the method of Hugenholz et al,[17] which assumes a constant LV mass throughout the cardiac cycle. First, LV mass (A) is calculated by the method of Troy et al[18] from end-diastolic LV dimension (B) and end-diastolic wall thickness (C), as follows: $A = 1.05[(B + 2D)^3 - (B)^3]$, where D = mean muscle thickness (with the assumption that C = D).

To calculate posterior wall thickness at end-systole (E), then: $1.05[(B + 2C)^3 - (B)^3] = 1.05[(F + 2E) - (F)^3]$ and, $E = 1/2[([B + 2C]^3 - [B]^3 + [F]^3)^{1/3}] - 1/2$ (F), where E = end-systolic posterior wall thickness and F is the measured echocardiographic LV end-systolic dimension.

Wall stresses were then determined at end-systole using a static thick-walled sphere model of the ventricle. Integrating pressure-generated force vectors perpendicular to the equatorial plane over the hemispheric surface of this model in spherical coordinates, the following relation can be shown: $S = PD/[4h(1 + h/D)]$, where S = equatorial wall stress, P = LV pressure, D = LV internal diameter, and h = LV posterior wall thickness. The stress was converted from millimeters of mercury to grams per centimeter by multiplying by 1.35. This figure was then converted to 10^3 dynes/cm^2 by multiplying by the gravitational constant 0.981×10^3 dynes/cm^2.[14,19]

Each patient had 4 total points, 1 at each of the 4 loading conditions plotted on a graph of end-systolic stress versus end-systolic volume index. Linear regression analysis by the least-squares method was done in each patient to determine the relation of end-systolic wall stress (independent variable) versus end-systolic volume index (dependent variable). Statistical analysis was done by analysis of variance performed on the data of the 4 groups with a modified nonpaired *t* test by the Bonferoni method.[20]

TABLE I Summary of Data in Adults

	Normal Subjects (n = 7)	Patients With SCA (n = 6)
Age (yr)	28 ± 7	31 ± 7
SVR	1,741 ± 343	856 ± 270*
EDVI	62 ± 8	106 ± 19*
CI	2.5 ± 0.5	5.0 ± 1.4*
EF	0.63 ± 0.07	0.59 ± 0.08
ESS/ESVI	2.8 ± 0.6	1.5 ± 0.4*
Slope of SI	3.3 ± 1.4	1.7 ± 0.6*

* $p < 0.05$.
Values are mean ± standard deviation.
CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; ESS/ESVI = resting end-systolic stress/end-systolic volume index ratio; SCA = sickle cell anemia; slope of SI = slope of Sagawa index derived from the linear regression of ESS/ESVI points from the 4 loading conditions; SVR = systemic vascular resistance.

Results

Loading conditions: The systemic vascular resistance was significantly lower in patients with SCA (Fig. 1, left). This value was 1,033 ± 314 dynes s cm^{-5} in patients with sickle cell anemia compared with 1,701 ± 314 dynes s cm^{-5} in normal patients ($p < 0.001$). When the data were examined by age, systemic vascular resistance in adult patients with SCA was significantly reduced to 856 ± 270 dynes s cm^{-5} compared with 1,741 ± 343 dynes s cm^{-5} in the control group (Table I) ($p < 0.05$). In children there were similar reductions in systemic vascular resistance with a value of 1,247 ± 216 dynes s cm^{-5} in patients with SCA compared with 1,663 ± 297 dynes s cm^{-5} (Table II) in the control group.

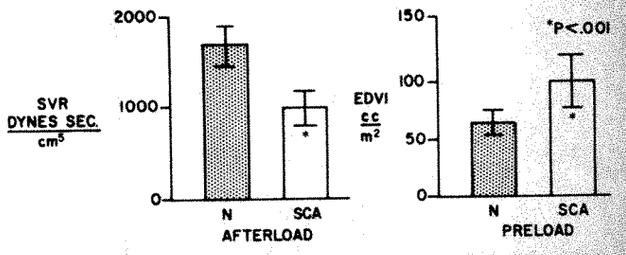

FIGURE 1. Loading conditions in 11 patients with sickle cell anemia (SCA) and 11 normal subjects (N). Afterload (**left**) as indicated by systemic vascular resistance (SVR) was significantly decreased in patients with SCA. Preload (**right**) as indicated by end-diastolic volume index (EDVI) was significantly increased in patients with SCA.

TABLE II Summary of Data in Children

	Normal Subjects (n = 4)	Patients With SCA (n = 5)
Age (yr)	10 ± 4	12 ± 4
SVR	1,663 ± 297	1,247 ± 216
EDVI	73 ± 10	96 ± 33
CI	3.6 ± 0.7	4.6 ± 0.8
EF	0.67 ± 0.07	0.59 ± 12
ESS/ESVI	2.5 ± 1.1	1.6 ± 0.8
Slope of SI	3.2 ± 1.1	2.0 ± 0.6

Values are mean ± standard deviation.
Abbreviations as in Table I.

Preload as indicated by end-diastolic volume was significantly increased to approximately twice the normal value in patients with SCA (Fig. 1, right). End-diastolic volume was increased to 102 ± 24 ml/m^2 in patients with SCA compared with 66 ± 10 ml/m^2 in control subjects ($p < 0.001$). In adult patients with SCA the end-diastolic volume index was 106 ± 19 ml/m^2 compared with 62 ± 8 ml/m^2 (Table I) ($p < 0.05$). In children with SCA similar results were noted, with the end-diastolic volume index being 96 ± 33 ml/m^2 compared with 73 ± 10 ml/m^2 in control subjects (Table II).

Ejection performance: Cardiac index was significantly increased in patients with SCA (Fig. 2, left), with a value of 4.7 ± 1.1 liters/min/m^2 compared with 2.8 ± 0.8 liters/min/m^2 in control subjects ($p < 0.001$). In adults the cardiac index was significantly increased to twice the normal value in patients with SCA, with a value of 5.0 ± 1.4 liters/min/m^2 compared with 2.5 ± 0.5 liters/min/m^2 in control subjects (Table I) ($p < 0.05$). In children similar results were again noted in patients with SCA, with the value of 4.6 ± −0.8 liters/min/m^2 compared with 3.6 ± 0.7 liters/min/m^2 in control subjects.

Ejection fractions were similar in the 2 groups (Fig. 2, right), with a value of 0.59 ± 0.09 in patients with SCA compared with 0.62 ± 0.07 in control subjects. In adults (Table I) and children (Table II) no significant differences in ejection fraction were noted between patients with SCA and control subjects.

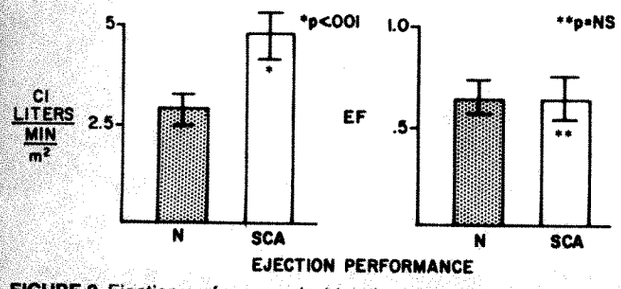

FIGURE 2. Ejection performance in 11 patients with sickle cell anemia (SCA) and 11 normal subjects (N). Cardiac index (CI) was significantly increased in patients with SCA. Ejection fraction (EF) was not significantly different in the 2 groups. NS = not significant.

Myocardial function: The ratio of resting end-systolic stress to end-systolic volume index was significantly reduced in patients with SCA (Fig. 3, left) to 1.5 ± 0.5 compared with 2.8 ± 0.6 in control subjects ($p < 0.001$). In adults with SCA the resting ratio of end-systolic stress to end-systolic volume index was 1.5 ± 0.4 compared with 2.8 ± 0.6 in adult control subjects (Table I) ($p < 0.05$). In children with SCA, again similar results were noted with a value of 1.6 ± 0.8 compared with 2.5 ± 1.1 in control children.

The average slope of the end-systolic stress versus end-systolic volume index relation derived from loading conditions in patients with SCA and control subjects is shown in Figure 3, right. The slope in patients with SCA was significantly reduced to 2.7 ± 1.3 compared with 4.4 ± 1.8 in control subjects ($p < 0.025$). In adults with SCA, the slope of the end-systolic stress-volume line was significantly reduced to 1.7 ± 0.6 compared with 3.3 ± 4.4 in normal adults (Table I) ($p < 0.05$). In children with SCA this slope was similarly reduced to 2.0 ± 0.6 compared with 3.2 ± 1.1 in control children (Table II).

Discussion

Our data suggest a significant depression of LV muscle contractile performance in SCA. This impaired myocardial function is independent of the duration of disease, because it is present in both children and adults. Increased preload and decreased afterload in patients with SCA may explain the normal ejection indexes of cardiac performance observed in this and previous studies.[6,21]

Symptoms of congestive heart failure were described in 85% of patients with SCA.[1] Although symptoms of heart failure led to the suspicion that myocardial contractile function was depressed in SCA,[4] symptoms and findings of congestive failure can be caused by circulatory congestion alone without depressed cardiac muscle function.[22–24] Knowledge of whether heart failure symptoms are due to circulatory congestion alone or to myocardial depression is of clinical importance. Vigorous infusion of fluids is recommended therapy in SCA.[25] Such therapy may lead to pulmonary edema.

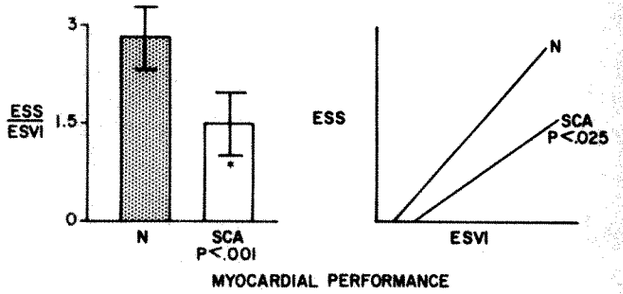

FIGURE 3. Myocardial performance in 11 patients with sickle cell anemia (SCA) and 11 normal subjects (N). **Left,** resting end-systolic stress/end-systolic volume index ratio (ESS/ESVI) was significantly decreased in patients with SCA. **Right,** the slope of the Sagawa line, derived from the linear regression of ESS/ESVI points from the 4 loading conditions, is significantly reduced in patients with SCA. The decrease in resting ESS/ESVI and in the slope of the Sagawa line suggests left ventricular dysfunction in patients with SCA.

Understanding the pathophysiology underlying the heart failure symptoms might form the basis of a more rational approach to the use of digitalis, diuretics, or vasodilators.

There have been 2 previous studies of ventricular performance in patients with SCA. Gerry et al[6] studied ejection phase indexes in 23 patients. They found the mean velocity of circumferential fiber shortening, ejection fraction, and systolic time intervals to be normal and concluded that SCA did not produce myocardial dysfunction.[6] Val-Mejias et al[21] also found that ejection fraction and systolic time intervals were normal in patients <23 years between sickle cell crises. In patients >23 years, the ejection fraction (0.66) was normal although significantly reduced from the control value (0.77). Systolic time intervals were prolonged in the older patients. They concluded that the chronic hemolytic process of SCA has a cumulative detrimental effect on myocardial function.[21]

Recent information on the effect of alterations in loading conditions on the ejection performance of the heart[9,12–16,21] indicates not surprisingly that studies using ejection indexes have not detected LV dysfunction in SCA. Ejection phase indexes are increased by decreases in afterload and increases in preload.[9,12,15,16,21] A decrease in afterload, systemic vascular resistance, and an increase in preload, end-diastolic volume index, were present in previous studies and in our patients with SCA (Fig. 1). Severe anemia can cause such changes.[8,9]

The end-systolic stress-volume relation proposed by Sagawa et al[26] is an index of contractile function independent of preload and a linear function of afterload, with the potential accurately to gauge contractile function in SCA despite the altered loading conditions. The Sagawa index was recently extended to man by Grossman et al[10] and Weisfelt et al.[27] Marsh et al[14] demonstrated that the end-systolic stress-volume relation can be determined in man by echocardiography.

We found the resting end-systolic stress end-systolic volume index and the slope of the Sagawa index decreased in our patients with SCA (Fig. 3). These findings suggest an intrinsic dysfunction of myocardial contractile function performance. We observed, as have others,[6,21] that load-dependent ejection phase indexes were normal or high; the indexes failed to detect myocardial dysfunction. As previously noted herein, myocardial dysfunction was independent of age. Consequently, dysfunction is probably not due to myocardial iron deposition, a process that would increase with age as the number of transfusions increased.

As cardiac muscle function is depressed in patients with SCA, positive inotropic drugs may have some value in patients with heart failure. Because a decrease in peripheral vascular resistance already exists, arterial vasodilators may not be helpful. Vigorous volume loading, the standard treatment for sickle cell crisis, in patients who already have an increased intracardiac volume and a decreased myocardial contractile function must be undertaken with caution.

The techniques we used have limitations. We employed M-mode echocardiography, in which only a single dimensional measure is used, to calculate ventricular volume. However, in subjects without dysnergic wall motion, echocardiography was found to provide accurate measurements of ventricular volume.[16] We have excluded ventricular wall dysnergy by 2-D echocardiography. Further, we calculated end-systolic pressure from peak-systolic pressure. Simultaneous intraarterial pressures and cuff pressures were recorded in 29 other patients and revealed a high degree of correlation between calculated end-systolic pressure and peak-systolic pressure measured by cuff. Finally, hand-grip exercise and amyl nitrite inhalation might have initiated baroreceptor reflexes, changing sympathetic stimulation to the heart, thus interfering with accurate assessment of contractile function. However, the lack of change in heart rate after our intervention and before our measurements indicates that this is unlikely.

The end-systolic volume/end-systolic pressure relation needs further validation as an independent index of contractility in the chronically volume- or pressure-overloaded heart, but several studies have found this index to correlate with other indicators of myocardial dysfunction in patients with chronic pressure and volume overload. In chronic volume overload due to aortic regurgitation[28] and in chronic pressure overload due to aortic stenosis,[29] the slope of the group end-systolic pressure relation was significantly reduced in patients with congestive heart failure compared with normal subjects or patients with severe aortic regurgitation or stenosis but no heart failure. Preoperative end-systolic volume was a predictor of postoperative LV performance in aortic regurgitation.[30] The preoperative end-systolic volume pressure relation was significantly depressed in patients who either died or continued to have heart failure after mitral valve replacement.[31]

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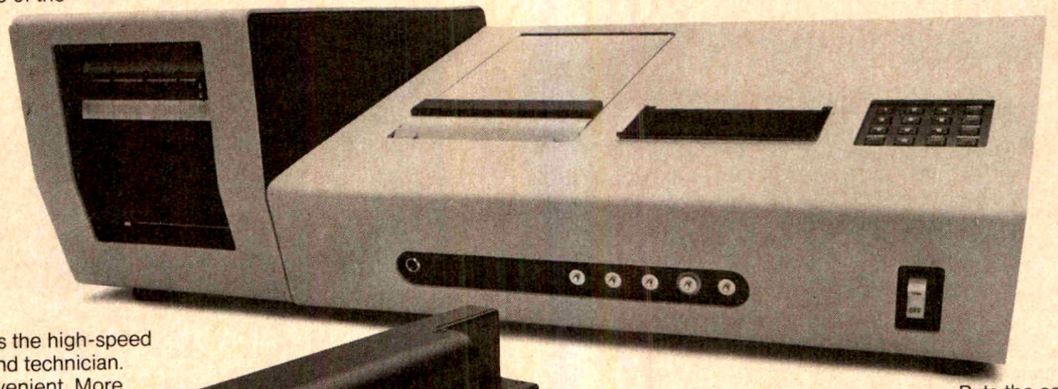

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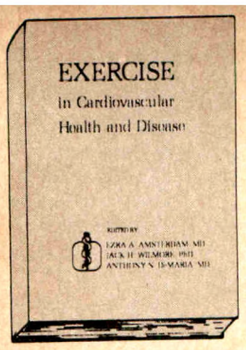

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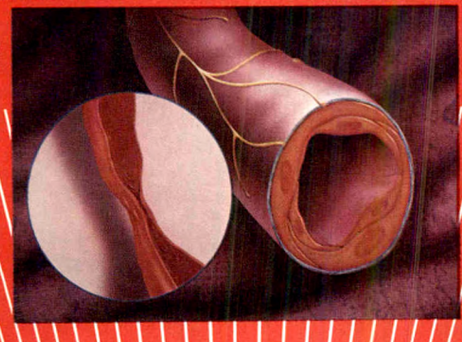

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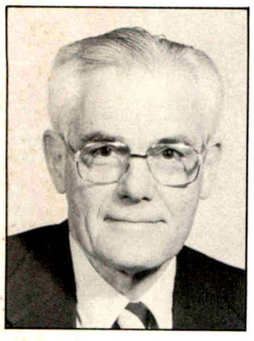

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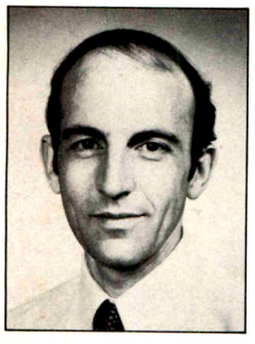

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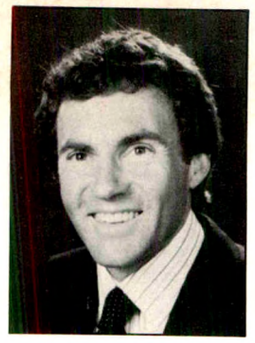

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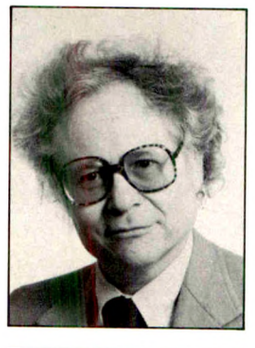

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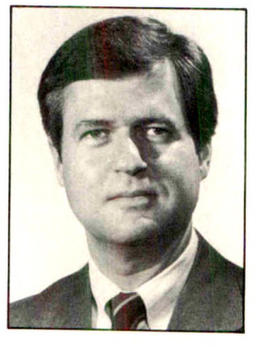

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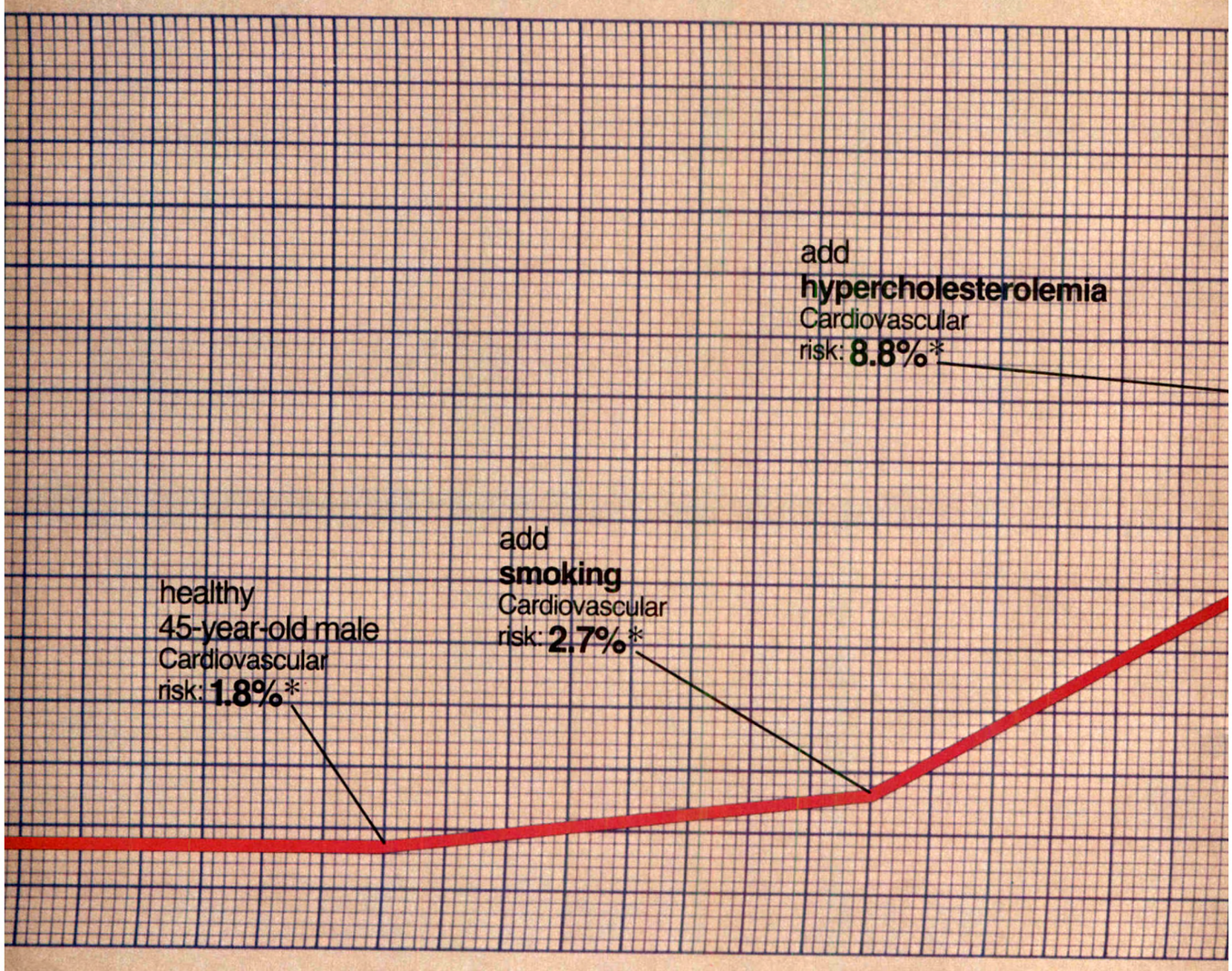

Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

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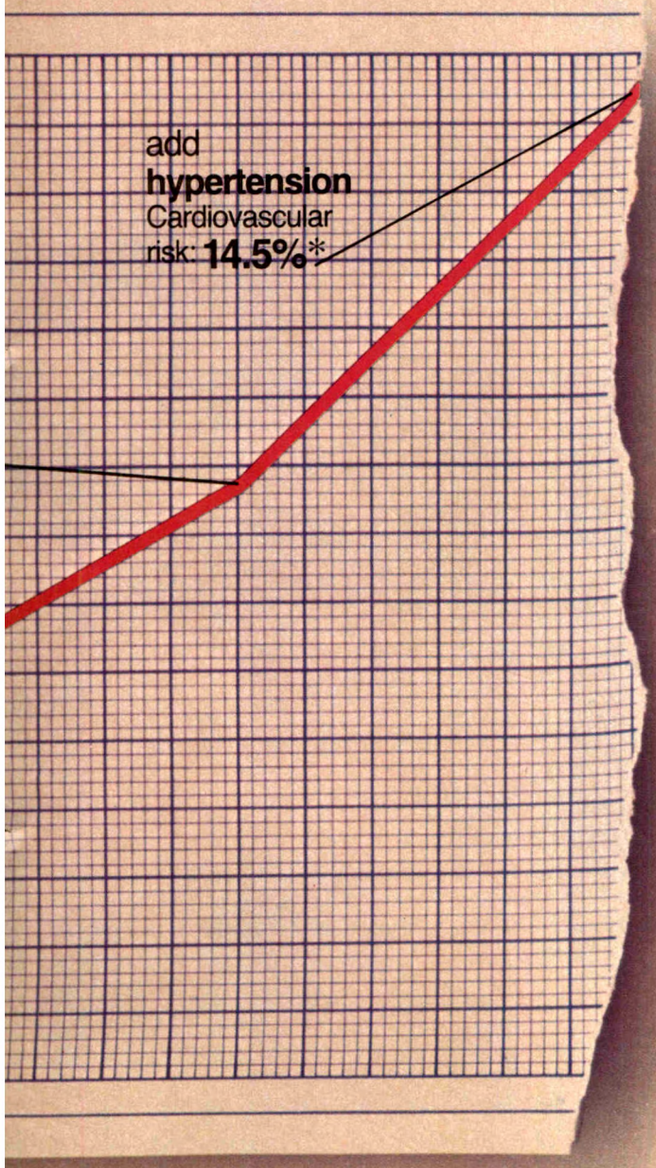

▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

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WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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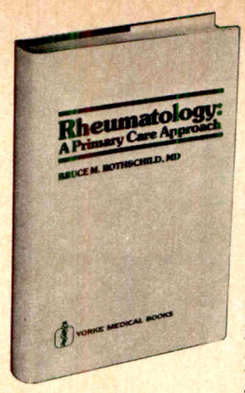

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Written by:

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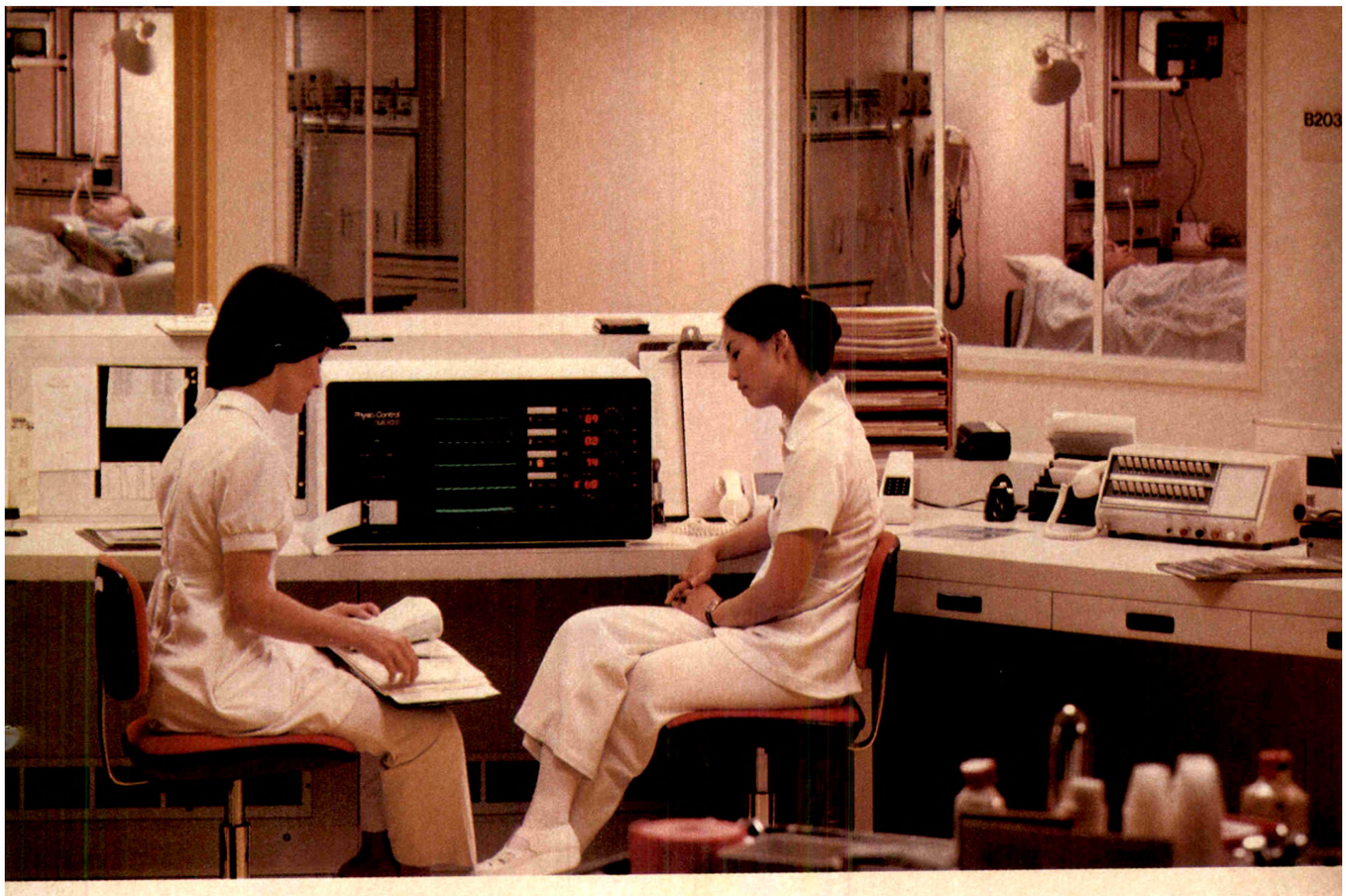

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Dynamic Evaluation of Prognosis From Time-Dependent Variables in Acute Myocardial Infarction

ERLING BIRK MADSEN, MD, PHILIP HOUGAARD, MS, and ELIZABETH GILPIN, MS

For predicting the 3 endpoints death, cardiac arrest, and cardiogenic shock within 44 days after admission for acute myocardial infarction (MI), a competing risk variant of the Cox multivariate model was developed. The population consisted of 1,140 patients with definite MI admitted within 24 hours of onset of symptoms. Prognostic variables from the entire hospitalization period were assessed. The time-dependent variables (occurrence of complications) were evaluated with occurrence up through the day before the actual prediction period started. The important prognostic variables for the endpoint death were ventricular fibrillation, age, congestive heart failure, and asystole. Variables for the endpoint cardiac arrest were congestive heart failure, ventricular premature beats, supraventricular tachycardia, extension of MI, and age. Variables for the endpoint cardiogenic shock were cardiac arrest, age, congestive heart failure, previous MI, and nodal rhythm. By using a hazard function for each endpoint and the coefficients for the variables entered, it is possible to estimate a total risk of death, cardiac arrest, or cardiogenic shock for the individual patient. This prediction can be updated during the course of hospitalization according to the occurrence of the new complications. The model can be directly utilized to assess risk.

Many factors have been found to have predictive value for short-term prognosis in patients with acute myocardial infarction (MI). Complications that can occur at any time during hospitalization have been incorporated if they occurred before a certain fixed day,[1–15] but dynamic treatment of these variables as time-dependent has been rare.[16] Because many variables are involved in prognostic evaluation after MI sometimes with strong interrelations, the utilization of multivariate methods such as discriminant function analysis,[2,4,7,11,13,15] multiple regression,[5,10] or Cox analysis[8,12] is essential. This study describes a new prognostic model in which information from time-dependent variables during the entire hospitalization period is evaluated dynamically for different endpoints.

Department of Cardiology, Glostrup Hospital and Statistical Research Unit, Danish Medical and Social Science Research Councils, Copenhagen, Denmark and Division of Cardiology, University of California, San Diego, California. This study was supported by the Danish Medical Research Council (12-0345), the Danish Heart Foundation, Copenhagen, Denmark, National Institutes of Health Research Grant HL 17682, Ischemic SCOR awarded by the National Heart, Lung, and Blood Institute, Bethesda, Maryland and International Research Fellowship 1 F05 TW0 3154-01, Fogarty International Center, U.S. Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland. Manuscript received January 6, 1983; revised manuscript received March 7, 1983, accepted March 8, 1983.

Address for reprints: Erling Birk Madsen, MD, Division of Cardiology, H-811A, University Hospital, 225 West Dickinson Street, San Diego, California 92103.

Material and Methods

Patients: The study population consisted of 1,140 consecutive patients with a definite MI admitted to our Coronary Care Unit during a 3-year period in 1977 to 1980. Their ages ranged from 23 to 92 years (mean 63) and 72% were men. All patients had MI <24 hours old at admission. For 813 patients with known time until admission the mean delay was 4.5 hours. A definite MI was diagnosed when at least 2 of the following criteria were present: typical severe chest pain, typical evolving electrocardiographic changes (Q waves or S-T segment/T-wave changes, or both), and elevated level of creatine kinase. Patients who died soon after the admission were included. The patients were routinely treated without prophylactic antiarrhythmic treatment, and beta-blocking agents were not given routinely. Cardiogenic shock was treated with pressor agents, and balloon counterpulsation was not available to us. No patient underwent coronary bypass surgery during the study period.

Prognostic variables: The following non–time-dependent variables were recorded: age, sex, previous MI (number), localization of MI (anterior [Q waves or S-T segment changes in any precordial lead] or other location), maximum creatine kinase (CK), and maximum CK-MB isoenzyme levels, measured at 6-hour intervals during the first 48 hours. The time-dependent variables analyzed were congestive heart failure (definite clinical signs of congestive heart failure [persistent pulmonary rales or enlarged neck veins or peripheral edema] or pulmonary vascular congestion from an x-ray in the upright position, or both), acute pulmonary edema, cardiogenic shock (systolic blood pressure <80 mm Hg or clinical signs of shock, or both), cardiac arrest (primary ventricular fibrillation or

TABLE I Univariate Analysis of Variables* for Death Within 44 Days

Variables	Total	Death (n)	Death (%)	p
Congestive heart failure	451	97	22	<0.0001
Cardiogenic shock	26	11	42	<0.0001
Ventricular fibrillation	67	19	28	<0.0001
Age (mean)	(61.1)	(67.9)		0.0001
Ventricular premature beats	181	35	19	0.0001
Atrial fibrillation	189	35	19	0.0002
Ventricular tachycardia	70	15	21	0.001
Nodal rhythm	72	15	21	0.005
Asystole	16	5	31	0.008
Atrioventricular block	53	12	23	0.009
Sex (female)	256	38	15	0.02
Previous MI	281	41	15	0.02
Pulmonary edema	69	12	17	0.07
Maximum CK (mean)	(1276)	(1482)		0.15
Location anterior	346	43	12	0.16
Maximum CK-MB (mean)	(264)	(329)		0.17
Supraventricular tachycardia	48	8	17	0.18
Extension of MI	21	4	19	0.22
Bradycardia	52	4	8	0.45
Ventricular rhythm	64	8	13	0.66
Total	957	101	11	. . .

* Occurrence of time-dependent variables (complications) within first 5 days.

For age, CK, and CK-MB, the mean (in units for enzymes) for survivors is indicated in total column.

CK = creatine kinase; CK-MB = creatine kinase isoenzyme; MI = myocardial infarction.

asystole of >10 seconds' duration), ventricular or supraventricular tachycardia (≥10 successive premature beats), ventricular premature beats (≥10% through more than 1 minute), atrioventricular block of second or third degree, nodal rhythm, sinus bradycardia (frequency <50 beats/min), atrial fibrillation or flutter, ventricular rhythm, and extension of MI (≥2 new of the 3 diagnostic criteria). For these variables the time of the first occurrence was noted and data from the entire hospitalization (usually about 18 days) were used for the analyses.

Prediction period: All patients were followed up for up to 44 days after admission. This period was chosen because our goal was to evaluate prognosis up to 14 days after discharge, which occurred at the latest around day 30. The time and cause of death were known for all patients who died. All deaths took place at the hospital or were witnessed and described as sudden death. Autopsy was performed in 90% of patients.

Statistical methods: As a preliminary step, all variables occurring before day 5 were tested univariately for association with mortality within 44 days after admission. Patients who did not survive until day 5 (183) were excluded from this analysis because prognostic variables in these patients are not relevant for the later outcome.

The multivariate analysis was the regression model proposed by Cox[17] describing the time to an endpoint (that is, death). The model was modified to a competing risks model with 3 endpoints within 44 days after admission[18]: death (i = 1), cardiac arrest (i = 2), and cardiogenic shock (i = 3). If more than 1 endpoint occurred the same day, the order was defined as cardiac arrest, cardiogenic shock, and death. The model for the hazard of endpoint i is $\lambda_z^i(t) = \lambda_0^i(t)e^{\beta_1^i Z_1(t)+\ldots+\beta_p^i Z_p(t)}$, where $\lambda_0(t)$ is an unspecified function common to all patients and $Z_1(t), \ldots, Z_p(t)$ are the covariates or prognostic factors (that is, age or complications). The values of $Z_1(t), \ldots, Z_p(t)$ have to be known at time t.

The regression coefficients (β_j^i) were estimated by a maximum partial likelihood method[19] and the integrated hazard functions ($\Lambda_0^i(t)$) by Breslow's method.[20] Only the significant

TABLE II Cox Analysis of the Most Important Univariate Variables for the Endpoint Death Within 44 days After Admission

	With Shock		Without Shock	
Variables	Coefficient	p	Coefficient	p
Age	0.041	<0.0001	0.077	<0.0001
VF	0.9	<0.0001	2.3	<0.0001
Heart failure	2.8	<0.0001	2.6	0.0001
Short-term shock	3.5	<0.0001	. . .	. . .
Late shock	1.0	0.003	. . .	. . .

The variable cardiogenic shock not included in the right portion because the patients were censored at the time of cardiogenic shock.

Late = risk beyond 5 days after the shock; p = p value from likelihood test; shock = cardiogenic shock; short-term = risk within 4 days after the occurrence of shock; VF = ventricular fibrillation.

variables were retained in the final model. To test the hypothesis that the regression coefficients were equal to zero (no prognostic importance), a likelihood ratio test statistic was used. Because of the overwhelming prognostic importance of cardiogenic shock, the survival after this complication was not described in the final model. The patients were censored after cardiogenic shock for all 3 endpoints and after cardiac arrest for the endpoint cardiac arrest only.

To assess prognosis, the risk (P_e) of at least 1 of the events (death, cardiac arrest, or cardiogenic shock) in the time period from day t to day 44 is as follows:

$$P_e = 1 - \exp\left(-\Sigma_{i=1}^{3}(e^{p_1^i Z_1(t)+\ldots+\beta_p^i Z_p(t)}(\Lambda_0^i[44] - \Lambda_0^i[t\text{-}1])\right).$$

For each endpoint (i) the difference in hazard rate (between day 44 and the day before day t) is multiplied by the exponential function of the score (sum of products $\beta_p Z_p$), given the assumption that the time-dependent covariates stay fixed. These 3 products are then added before the exponential function of the negative value of the sum gives the total risk.

To evaluate the importance of the last day in the observation period 2 analyses were performed. First, we included information on the occurrence of time-dependent variables (complications) through the day when the prediction period began (time t). We repeated the analyses with the time-dependent variables included only up to the day before prediction commenced (time t-1). This approach allowed evaluation of any connection between the timing of some variables and the endpoints.

Results

Univariate results for endpoint death: The univariate importance of the prognostic variables occurring during the first 5 days for the 957 patients who survived day 5 is shown in Table I. The most important variables (smallest p values) were congestive heart failure, cardiogenic shock, ventricular fibrillation, age, and ventricular premature beats. Twelve variables were univariately significant.

Multivariate results for endpoint death: In our first analysis we included only the most important univariate variables (congestive heart failure, cardiogenic shock, ventricular fibrillation, and age) in the Cox model. The left part of Table II shows the regression coefficients for these variables. The largest coefficient belonged to cardiogenic shock, which implied an especially high risk of death in the first 4 days after shock ($e^{3.5}$ = 33 times greater risk compared with patients

TABLE III Coefficients for Other Variables When Entered Into The Cox Analysis

Variable	Coefficient	SD	p
Asystole	1.1	0.3	0.0001
Infarct localization (anterior)	0.4	0.1	0.01
Atrioventricular block	0.6	0.3	0.03
Bradycardia	−1.4	0.7	0.05
Maximum CK-MB (0-2000)	0.0006	0.0004	0.15
Pulmonary edema	−0.4	0.3	0.20
Atrial fibrillation	0.2	0.2	0.26
Previous MI	0.07	0.08	0.33
Ventricular premature beats	−0.2	0.2	0.33
Extension of MI	−0.3	0.4	0.52
Ventricular tachycardia	−0.2	0.3	0.56
Maximum CK (64-15,200)	0.00003	0.00007	0.62
Sex (female)	−0.04	0.14	0.78
Supraventricular tachycardia	0.0	0.3	0.89
Nodal rhythm	0.0	0.3	0.92
Ventricular rhythm	0	0.4	0.93

Variables entered one at a time in addition to age, ventricular fibrillation, and heart failure.
For CK and CK-MB range in units indicated in parentheses.
SD = standard deviation for coefficient; other abbreviations as in Table I.

TABLE IV Final Cox Model for Risk of Death, Cardiac Arrest, and Cardiogenic Shock

Variable	Coefficient	SD	p
Death			
Ventricular fibrillation	2.7	0.2	<0.0001
Age	0.082	0.010	<0.0001
Congestive heart failure	2.3	0.6	0.0001
Asystole	3.4	0.5	0.01
Constant	−4.9	. . .	. . .
Cardiac Arrest			
Congestive heart failure	2.2	0.4	<0.0001
Ventricular premature beats	0.9	0.2	0.0001
Supraventricular tachycardia	1.0	0.3	0.001
Extension of MI	1.0	0.5	0.03
Age	0.010	0.007	0.12
Constant	−0.6	. . .	. . .
Cardiogenic Shock			
Cardiac arrest	1.2	0.17	<0.0001
Age	0.028	0.007	<0.0001
Congestive heart failure	3.3	1.0	0.001
Previous MI	0.22	0.07	0.003
Nodal rhythm	0.8	0.3	0.01
Constant	−1.7	. . .	. . .

Abbreviations as in Tables I and III.

without shock). Beyond the first 5 days after shock, the risk diminished to about 3 times that of patients without shock. The coefficients for the other variables indicated 16 times increased risk if congestive heart failure occurred and 2.5 times increased risk if ventricular fibrillation occurred.

The repeated analysis when cardiogenic shock was not included as a variable showed that age and ventricular fibrillation had increased coefficients, indicating the greater prognostic importance of these variables (Table II, right portion).

Next, all the remaining variables were entered in the analysis one at a time in addition to the important variables excluding cardiogenic shock. The coefficients for the added variables ordered according to the p value are presented in Table III. Only asystole, infarct localization, and atrioventricular block were significant and could contribute prognostic information to the ones already selected. Some of the univariately significant variables were not significant in the Cox analysis because of interrelations with variables that were better predictors. Pulmonary edema, ventricular premature beats, extension of MI, and ventricular tachycardia all had negative coefficients. However, these coefficients were all near zero.

When asystole, localization, and atrioventricular block were included in the model, only asystole retained significance. Table IV (top) shows the final model for the endpoint death. Only 4 variables were retained: ventricular fibrillation, age, congestive heart failure, and asystole.

Endpoint cardiac arrest: The left part of Table V shows the variables selected for the endpoint cardiac arrest when occurrence of the time-dependent variables were included through the day beginning the prediction period. For example, if prediction was for day 7 to day 44, the variables could occur from day 1 through day 7. The most significant variables for this endpoint were ventricular tachycardia, congestive heart failure, and ventricular premature beats.

The right portion of Table V shows the results when the variables were included only up to the day before the

TABLE V Variables Selected for Endpoint Cardiac Arrest

	Through Actual Day*		Through Previous Day†	
Variables	Coefficient	p	Coefficient	p
VT	1.5	<0.0001	−0.2	0.60
Heart failure	2.1	<0.0001	2.2	<0.0001
VPB	0.7	0.0001	0.9	0.0001
Extension of MI	1.3	0.0004	1.1	0.03
AV block	0.7	0.0005	0.4	0.28
SVT	0.6	0.03	1.1	0.001
Age	0.007	0.33	0.011	0.10

* Variables included with occurrence through the day (t) when the prediction period began.
† Variables included with occurrence only through the day before the prediction period began (t-1).
AV = atrioventricular; SVT = supraventricular tachycardia; VPB = ventricular premature beats; VT = ventricuiar tachycardia; other abbreviations as in Table I.

TABLE VI Variables Selected for Endpoint Cardiogenic Shock

	Through Actual Day		Through Previous Day	
Variables	Coefficient	p	Coefficient	p
Pulmonary edema	1.0	<0.0001	0.2	0.56
Cardiac arrest	0.9	<0.0001	1.2	<0.0001
AV block	0.8	0.0002	0.2	0.65
Age	0.021	0.001	0.028	<0.0001
Previous MI	0.24	0.002	0.22	0.003
Heart failure	3.1	0.003	3.2	0.002
Nodal rhythm	0.6	0.004	0.7	0.02
VT	0.4	0.04	0.3	0.38

Abbreviations as in Tables I and V.

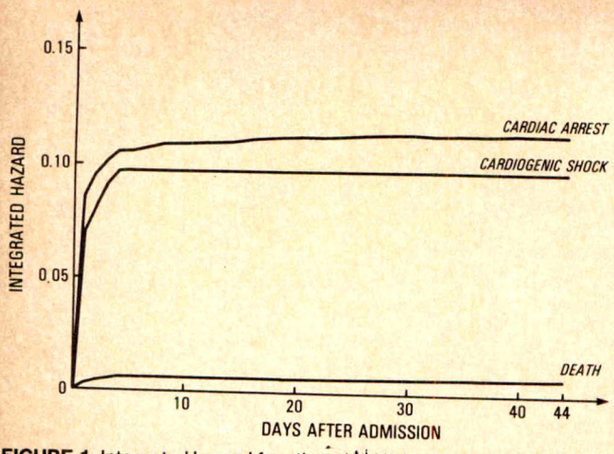

FIGURE 1. Integrated hazard functions ($\Lambda_0^1(t)$) for the endpoints death, cardiac arrest, and cardiogenic shock within 44 days after admission.

start of the prediction period. For this example the variables could occur from day 1 through day 6. This modification was associated with major changes in coefficients and p values for some of the variables. Ventricular tachycardia and atrioventricular block lost significance. Supraventricular tachycardia increased in importance. Therefore, ventricular tachycardia was indicative of a cardiac arrest during the day starting the prediction interval but not for a later cardiac arrest.

The final model for the endpoint cardiac arrest after deletion of the nonsignificant variables for the analysis up to but not including the start of the prediction interval is presented in Table IV (middle). Only 5 variables were retained. Age was retained even though it was not significant.

Endpoint cardiogenic shock: Table VI presents in the same manner as Table V the analyses for the endpoint cardiogenic shock. The most significant variables in the first analysis were pulmonary edema, cardiac arrest, and atrioventricular block. When only variables up to the day before the beginning of the prediction interval were included, pulmonary edema, atrioventricular block, and ventricular tachycardia lost their importance altogether. This indicates that these complications often occurred earlier on the same day as cardiogenic shock and were not prognostically important for later shock. The importance of cardiac arrest increased, while the coefficients and p values for the other variables were relatively unchanged.

The final model for the endpoint cardiogenic shock (Table IV, lower part) shows that only 5 variables were retained. Here age was significant, and the most important other variables were cardiac arrest and congestive heart failure.

Risk estimation: The integrated hazard functions for each endpoint (death, cardiac arrest, and cardiogenic shock) are illustrated in Figure 1. After steep increases in the first few days after the admission, the rate of increase slowed. By using the coefficients from Table IV on data for the individual patient according to the occurrence of the relevant variables, it is possible to compute an estimate of the risk for the 3 endpoints up to day 44 after admission. This risk assessment can be updated dynamically according to changes in the important variables and in the hazard functions.

For a 60-year-old patient surviving day 5 without any complications $e^{\beta_1^1 Z_1 + \ldots + \beta_p^1 Z_p} = e^0 = 1$ and the integrated hazard difference from day 5 to day 44 (Fig. 1) is 0.009 for cardiac arrest, 0.005 for cardiogenic shock, and 0.001 for death. The risk of an event from day 5 to day 44 is $1 - \exp[-(0.009 + 0.005 + 0.001)] = 1.5\%$. The computation can be accomplished by an appropriately programmed calculator.

Discussion

How to deal with time-dependent variables is an important question in the evaluation of prognosis after MI. This model incorporated the most important prognostic variables for 3 competing endpoints (death, cardiac arrest, and cardiogenic shock) (Table IV) with changing risk of each endpoint as indicated by the integrated hazard function (Fig. 1). The risk could be updated during the hospitalization according to the occurrence of new complications.

Multivariate importance: Only 4 of 12 univariately significant variables for the endpoint death (Table I) were found to be important independent predictors in the multivariate Cox analysis. This confirms the importance of using multivariate methods.[2,4,5,7,10–13,15] The Cox model as used previously for short-term prognostic evaluation[8,12] utilizes the observation time to the endpoints in the prediction period and directly provides a computed estimate of the risk of events.

The historical variables age, sex, and previous MI were univariately important, but only age was selected in the Cox analyses. Therefore, the dynamic prognostic variables incorporates prognostic information from the historical variables that are not independently important. It is not necessary to include the historical variables in a prognostic scheme if the dynamic variables are taken into account.

Time-dependence: Previous studies have mostly used a fixed point in time for prognostic evaluation such as day 1,[6,9,11,13,14] day 2,[10,15] day 5,[12] or discharge from the hospital.[2,3,5,7,8] Only 1 report tried to evaluate the prognosis in a simple dynamic way by calculating a risk score each day.[16]

The period of time in which the variables are included influences which variables are selected by the analysis, particularly if certain variables precede endpoints on the same day. In this material this occurred with ventricular tachycardia and atrioventricular block for the endpoint cardiac arrest (Table V) and with pulmonary edema, ventricular tachycardia, and atrioventricular block for the endpoint cardiogenic shock (Table VI). It is probably most feasible and practical clinically if the variables are evaluated only up to the day before the beginning of the prediction interval.

Endpoints: No previous study of prognosis after MI has reported using endpoints other than death with separate hazard functions for each. Our analysis indicated that a different set of variables and coefficients were of prognostic importance for the 3 competing endpoints. The endpoint death alone is not sufficient

for the prognostic evaluation. Identification of patients at high risk of cardiac arrest is especially important when early discharge is being considered.

Comparison with previous studies: It is difficult to compare our findings with those of previous studies because of their different statistical methods and approaches. The only comparisons feasible are for the important prognostic variables in the different studies.

For the endpoint death, our prognostic variables have had prognostic importance in several previous studies. Despite definition differences, congestive heart failure has been a consistent prognostic finding.[1–4,6–8,10–12,15,16] Cardiac arrest was important in 5 previous studies.[7,11,21–23] Age was an important variable in studies without restriction according to age.[7,8,12]

Congestive heart failure,[24,25] supraventricular tachycardia,[24] ventricular premature beats,[24,25] and extension of MI[24] have all been well documented to be indicative of later cardiac arrest. In contrast to previous studies,[24,25] ventricular tachycardia was not selected for the endpoint cardiac arrest in the final model in our study, but it was indicative of a cardiac arrest occurring later the same day (Table V).

A previous univariate study[26] confirmed that age, heart failure, cardiac arrest, and nodal rhythm were indicative for the later development of cardiogenic shock.

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Prevalence and Prognosis After a First Nontransmural Myocardial Infarction

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Prevalence, prognosis, and coronary anatomy associated with nontransmural myocardial infarction (MI) were prospectively assessed in 458 consecutive men admitted to our coronary care unit with a first MI. Cardiac catheterization was performed in 402 of the 436 survivors within 1 month of the acute event. Mean follow-up was 33 months (range 5 to 72). Nontransmural MI was diagnosed in 28 patients (6%). These patients were younger (46 ± 10 versus 51 ± 7 years, p <0.001) and had lower peak creatine kinase values (601 ± 319 versus 1,141 ± 923 U, p <0.01) and better ejection fraction (63 ± 8 versus 46 ± 14, p <0.001) than did their counterparts. Survivors of nontransmural MI also had fewer affected arteries (p <0.001) and a lower prevalence of total or subtotal occlusion (>90%) in the involved artery (p <0.01). Mortality in the acute phase and long-term survival at 4 years (Kaplan-Meier) in patients with nontransmural MI (94%) were similar to those in patients with transmural MI (90%). The occurrence of new nonfatal coronary events was also similar in both groups of MI survivors. Thus, in the absence of symptoms, more aggressive management to improve survival does not seem warranted after nontransmural MI.

Despite extensive investigation, the prognostic significance of nontransmural myocardial infarction (MI) remains controversial.[1–10] Although some studies report a lower in-hospital mortality in patients with nontransmural MI than in those with transmural MI,[6,7] others found the same mortality in both forms of MI.[3,4,11] Similarly, the long-term mortality of patients with nontransmural MI has been either comparable to[3,6] or greater than[4] that of patients with transmural MI. Discrepancies among series available for review may be due to the criteria used to select patients for study. In particular, the inclusion of patients with healed MI[3,4,6,9–11] is misleading because the electrocardiogram is a poor predictor of transmural involvement in the presence of scar tissue.[12–14] Because left ventricular and coronary angiography were not performed routinely, previous studies failed to characterize baseline variables that appear to be important predictors of survival after MI.[2,15–19]

This investigation elucidates the prognostic significance of a first nontransmural MI. A series of 402 consecutive patients with proven MI were catheterized within 1 month of the acute event; 24 of these patients had nontransmural MI and are the subject of this report.

Methods

Patient population: From December 1975 to September 1981, 458 men aged ≤60 years were admitted to our Coronary Care Unit with a first MI. A detailed description of the prospective protocol, the University of Barcelona Myocardial Infarction Research Project, appears elsewhere.[15,20]

Criteria for diagnosis of MI: Acute MI was diagnosed when ≥2 of the following criteria were present: ischemic chest pain lasting >20 minutes, a typical increase and decrease in enzyme levels (total creatine kinase, lactic dehydrogenase [LDH], and LDH isoenzymes) and evolving Q-wave abnormalities with acute ST-T wave changes on the electrocardiogram. Previous MI was diagnosed in the presence of a hospital admission for documented MI or Q waves in the electrocardiographic diagnosis of an old infarct.

Nontransmural MI was diagnosed when a normal QRS persisted throughout the hospital stay (according to the

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TABLE I Population

		Survivors	
	Non-survivors	Non-catheterized	Catheterized
Number	22	34	402
	p <0.01		
Age (yr)	54 ± 5	p <0.05 51 ± 7	50 ± 7
	p <0.05		
CK	1,483 ± 990	916 ± 706	1,131 ± 900
	p <0.001		
CHF at CCU	11	1	24
MI location			
Anterior	11	10	152
Inferior	9	16	193
Combined	2	4	33
Nontransmural	0	4	24

CK = creatine kinase, peak value; CHF = congestive heart failure; CCU = coronary care unit; MI = myocardial infarction.

TABLE II Clinical and Angiographic Findings in Patients With Myocardial Infarction

	Nontransmural	Transmural	p Value
Number	24	378	
Age (yr)	46 ± 10	51 ± 7	0.001
Absence of "risk factors"	15 (53%)	130 (34%)	0.05
Creatine kinase (peak)	601 ± 319	1,141 ± 923	0.01
Death at CCU	0	22	NS
Severe CHF at CCU	0	24	NS
LVEDP	10 ± 5	14 ± 7	0.01
Ejection faction	63 ± 8	46 ± 14	0.001
Coronary arteries (n) narrowed ≥50%			
0	7 (29%)	21 (6%)	0.001
1	9 (37%)	138 (36%)	NS
2	4 (17%)	129 (34%)	NS
3	4 (17%)	90 (24%)	NS

CCU = coronary care unit; CHF = congestive heart failure; LVEDP = left ventricular end-diastolic pressure; NS = not significant.

Minnesota Code[21]) and peak enzyme levels were at least twice the baseline.

Clinical evaluation: On admission all patients underwent careful investigation of their risk factors. Each patient was questioned to determine a history of coronary artery disease and the use of cigarettes. Diabetes mellitus was considered present if the patient was being treated for this condition or if the fasting blood sugar was >120 mg/100 ml (6.7 mmol/liter). Similarly, hypertension was diagnosed if the patient was already receiving antihypertensive drugs or if the blood pressure was >155/95 mm Hg. Serum cholesterol and triglyceride levels were measured after a 12-hour fast in all patients; if either was elevated, hyperlipidemia was diagnosed. Obesity was defined as a weight ≥15% above that considered ideal for a given height.

Catheterization and angiographic procedures: Within 4 weeks of MI, coronary angiography was performed in 402 of the 436 survivors. The remaining 34 patients (4 with nontransmural infarct) were excluded because of their refusal to undergo catheterization (23 patients), coexistence of a disease with decreased life expectancy (2 patients had cancer, 3 cerebrovascular accidents, and 4 severe cor pulmonale), or dye allergy.[1] Informed consent was obtained in all patients before catheterization.

Left ventricular volumes and ejection fraction were determined using the area-length method modified for single-plane calculations.[22] To assess regional wall motion, 5 areas of interest, anterobasal, anterolateral, apical, diaphragmatic, and posterobasal, were constructed by drawing a longitudinal axis from the midpoint of the aortic valve to the apex and trisecting it by 2 equidistant chords. The 2 apical areas were combined and treated as a single region. The systolic change for each region was measured as the segmental ejection fraction.[23]

All angiograms were assessed by 2 independent observers that coded the degree and location of coronary arterial lesions. Discrepancies were resolved by caliper measurement of percent reduction of luminal diameter in the projection showing maximal stenosis. Lesions <50% were considered nonobstructive. Each patient was classified as having 1-, 2-, or 3-vessel coronary artery disease. Obstruction of diagonal or marginal branches was considered a lesion of the left anterior descending or circumflex artery, respectively. Collaterals were judged to be well developed when the diameter of the receiving artery measured >1 mm and the sending vessel showed nonobstructive lesions.[20]

Follow-up: Patients were seen monthly during the first 3 months and every 3 months thereafter. Clinical status, results of physical examination, and a resting electrocardiogram were recorded at each visit. The mean follow-up was 33 months (range 5 to 72). Follow-up was completed in 372 of the 402 patients who had angiograms; the other patients were lost to follow-up. Although no attempt was made to standardize medical treatment, all patients were kept on a low-cholesterol diet and moderate exercise was recommended. Surgical treatment was reserved for intractable angina or lesions of the left main coronary artery.

Statistical analysis: A total of 12 variables were identified in each patient from the clinical history and cardiac catheterization and angiographic data. These variables were age, history of hypertension, dyslipemia, diabetes, peak creatine kinase value, peak LDH, infarct location, severe congestive heart failure (Killip's class III or IV) complicating the acute phase of the infarct, left ventricular end-diastolic pressure, ejection fraction, number of abnormally contracting segments, and the number of involved vessels. Differences between patients with transmural and nontransmural MI were analyzed using the Statistical Package for Social Sciences, applying Student's *t* test, Fisher's exact test, or chi-square when appropriate. Occurrence of new coronary events was compared between patients with and without nontransmural MI by constructing Kaplan-Meier actuarial curves for the 2 groups. Statistical differences were assessed by the log-rank test. A p value <0.05 was considered significant. Patients not accepting coronary angiography were excluded from survival analysis.

Results

Prevalence: Of the 458 patients admitted to our Coronary Care Unit with a first infarction, 28 had nontransmural MI according to our criteria. Therefore, subendocardial infarct was prevalent in 6% of patients in the present series.

Clinical findings: None of the 28 patients with subendocardial infarct and 22 with transmural necrosis died in the acute phase, the difference being not statistically significant. Nonsurvivors were older and had higher peak creatine kinase values and a higher prevalence of severe congestive heart failure (Table I).

Patients with nontransmural MI were younger (46 ± 10 versus 51 ± 7 years, p <0.001) and had lower creatine kinase levels (601 ± 319 versus 1,141 ± 923 U, p <0.01)

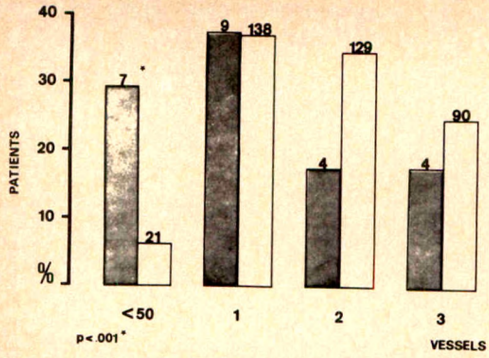

FIGURE 1. Percentage distribution of the number of affected vessels (≥50% stenosis) in patients with transmural infarcts (**open bars**) and those with nontransmural necrosis (**shaded bars**). As shown, nonobstructive disease was more prevalent among the latter group, and multivessel disease (2 and 3 vessels) in the former ($p < 0.01$).

in the acute phase than did patients with transmural involvement. Although no differences were found in the prevalence of a history of hypertension, diabetes, or cigarette consumption, the absence of all risk factors was more common among patients with nontransmural MI ($p < 0.05$) (Table II). Of the 436 acute-phase survivors, 402 (378 with transmural and 24 with nontransmural MI) underwent cardiac catheterization within 1 month of the onset of symptoms.

Hemodynamic and angiographic findings: Left ventricular end-diastolic pressure was lower (10 ± 5 versus 14 ± 7 mm Hg, $p < 0.01$) and ejection fraction higher (64 ± 8 versus 46 ± 14%, $p < 0.001$) in patients with nontransmural MI. No patient in this group was found to have an ejection fraction lower than 50%. Regional wall motion analysis showed that patients with subendocardial infarction had fewer abnormally contracting segments (0.73 ± 0.93 versus 2.29 ± 1.43, $p < 0.001$) and a higher prevalence of normal left ventricular angiograms (50 versus 9%, $p < 0.001$) than did survivors of transmural infarction.

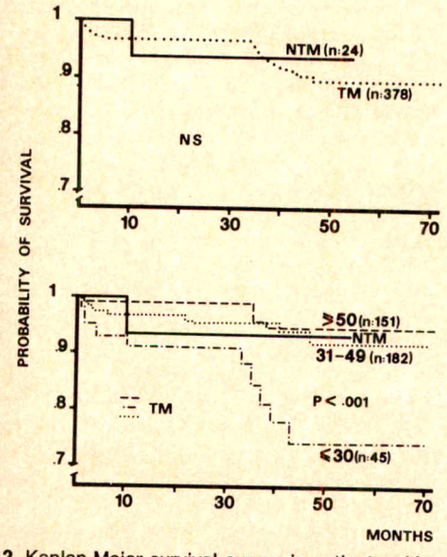

FIGURE 2. Kaplan-Meier survival curves in patients with transmural and nontransmural myocardial infarction. The **upper panel** shows similar long-term survival in both populations (90 and 94% at 4 years, respectively). The **lower panel** shows that the probability of survival after a first nontransmural myocardial infarction (all patients having an ejection fraction of 50%) is similar to that in patients with comparable degrees of left ventricular dysfunction after a first transmural infarction (4-year survival in the latter group was 95% for those with an ejection fraction of 50%, 92% for those with an ejection fraction between 31 and 49%, and 75% for those with an ejection fraction <30%).

TABLE III Location of Total or Subtotal Coronary Arterial Narrowings in Patients With Nontransmural and Transmural Myocardial Infarction

Coronary Artery	Nontransmural (n = 10 [41%])	Transmural (n = 285 [76%])	p Value
Left main	0	2	NS
LAD (proximal-mid)	3	125	NS
LC (proximal)	1	17	NS
Right (proximal-mid)	1	86	NS
Distal LAD, LC, right, diagonal, or marginal	5	55	0.05

LAD = left anterior descending; LC = left circumflex; NS = not significant.

Figure 1 shows the number of involved arteries (stenosis ≥50%) in both groups of infarct survivors. Patients with nontransmural MI had a higher prevalence of nonobstructive disease (29 versus 6%, $p < 0.001$), 4 of them having strictly normal coronary angiograms. Multivessel disease was prevalent among survivors of a transmural infarct (59 versus 33%, $p < 0.05$). The presence of total or subtotal (>90%) stenosis in ≥1 coronary arteries was also more common among the latter (76 versus 41%, $p < 0.01$). In 5 of 10 patients with nontransmural MI and stenosis >90% in the corresponding artery, the lesion was located in either a marginal or diagonal branch or the distal segment of a major artery (Table III). No differences were found in the prevalence of well-developed collaterals between the 2 groups.

Follow-up: No patient surviving a nontransmural MI and 20 in the group with transmural infarct had a nonfatal reinfarction, a statistically nonsignificant difference. The incidence of new onset of angina was also similar in both groups (42 and 37%, respectively). In no patient in the group with subendocardial infarction and in 46 with transmural infarcts did congestive heart failure develop during follow-up, a nonsignificant difference ($p = 0.06$).

Figure 2 shows Kaplan-Meier actuarial curves in survivors of transmural and nontransmural infarcts (4-year survival was 90 and 94%, respectively). No differences were found when both populations were compared (upper panel). When survival curves were constructed according to ejection fraction subsets in patients with transmural infarct, survivors of subendocardial infarct behaved like their counterparts with transmural necrosis and mild or moderate left ventricular dysfunction (lower panel).

TABLE IV Representative Studies on Long-Term Follow-Up After Nontransmural Myocardial Infarction (MI)

First Author (yr)	n	Prospective	Angiographic Data	Previous MI (%)	Previous Angina (%)	Prevalence of Nontransmural MI (%)	1-Year Mortality (%)	Reinfarction Rate (%)
Madigan et al[1] (1975)	50	0	+	24	66	...	6	22
Cannom et al[4] (1976)	188	+	0	32	85	21	20	26
Schultze et al[2] (1978)	48	0	+	41	...	...	...	...
Szklo et al[6] (1978)	1,236	+	0	34	23	29	16	...
Mahony et al[10] (1980)	635	+	0	0	25	4	0	...
Marmor et al[9] (1981)	200	+	0	20	18	29	12	43
Hutter et al[8] (1981)	67	0	0	46	72	...	35	23
Present series	458	+	+	0	23	6	0	0

Discussion

Prevalence: It is now well recognized that minor degrees of myocardial necrosis can occur in a subset of patients with unstable angina pectoris.[24–28] Because differentiation between nontransmural infarct and unstable angina relies on the sensitivity of the test used for diagnosis, the wide discrepancies in survival patterns found in the literature are expected. If our criteria for the diagnosis of MI had been less stringent or if more sophisticated techniques (such as technetium scanning) had been used, our series would have included many patients now diagnosed and treated in this institution as having unstable angina pectoris.

Our data indicate that only 6% of patients with a first MI will fulfill the electrocardiographic and enzymatic criteria of nontransmural infarct. This figure is at variance with previous data reporting the prevalence of nontransmural infarct to be higher. Szklo et al,[6] in a retrospective multicentric study, found an incidence of 29%, whereas higher figures (up to 40%) have been reported in other studies dealing with selected population samples.[4,7] A source of error in estimating the prevalence of nontransmural MI may stem from the inclusion of patients with a previous MI. As in Table IV, most series include large percentages of patients with previous MI. Indeed, pathologic studies show that a new transmural MI may fail to produce diagnostic Q waves in the presence of an old scar.[12,29] Interestingly enough, Mahony et al[10] in the only study excluding patients with previous MI found that 4% of patients with acute MI failed to develop significant QRS abnormalities.

Results in prospective studies may vary depending on the population, the age and sex of the patients, and the selection criteria. Although we chose an age limit of 60 years to increase the likelihood of long-term follow-up, our series included 70% of all patients hospitalized with MI. Female subjects were excluded to increase the uniformity of the sample, as infarction in women is still uncommon in this country. In fact, only 23 women <60 years of age were hospitalized with acute MI during the study (male/female ratio 19:1). However, the incidence of symptomatic arterial disease in women parallels that in men, with a time lag of 8 to 10 years.[29,30] Thus, our results should not be seriously distorted by the exclusion of women.

Clinical and angiographic characterization of nontransmural MI: We found that patients with nontransmural infarcts were younger ($p < 0.001$) and had a higher ejection fraction ($p < 0.001$) and fewer affected ventricular segments ($p < 0.001$) than did patients with transmural infarcts. These data and the finding of a lower peak creatine kinase value in the former group suggest that the infarct is smaller in nontransmural MI. This hypothesis is in contrast to previous reports[1–3] in which no differences were found in the severity of left ventricular dysfunction between the 2 groups. Again, the exclusion of patients with previous infarction (which represents as much as 30% of all cases in some series[6]) might account for the observed differences.

Marmor et al[9] recently reported a wide prevalence of early reinfarction in patients with subendocardial infarcts (43 versus 8% in patients with transmural necrosis). In that study, serial plasma MB-CK isoenzyme activity was determined for 14 days and recurrences were elegantly demonstrated by secondary plasma MB-CK peaks. Nevertheless, repeat chest pain and new ST-T wave changes were found to be sensitive markers of early reinfarction (90 and 80% sensitivity, respectively). Accordingly, recurrent necrosis is unlikely to be missed in the present series despite the fact that we did not routinely assess plasma enzyme activity for a longer interval than clinically required. Thus, the discrepancies found between our data and those of Marmor et al[9] might be ascribed to differences in criteria of patient selection, as suggested by the finding that recurrences were more common in women than in men.

The prospective design of our study allows estimation of the coronary anatomy associated with nontransmural MI. We found nonobstructive disease in 7 of these patients (29%), a significantly higher incidence than that found among survivors of transmural infarcts (6%). The prevalence of total or subtotal occlusion of the involved artery was lower in patients with nontransmural MI. In addition, in 5 of the 10 patients with nontransmural infarction showing total or subtotal occlusion of a coronary artery, the lesion was located in a marginal or diagonal branch or in the distal segment of a major coronary artery. We recently found[20] that patients with stenosis of ≤90% in the artery corresponding to a MI showed better ejection fraction and regional wall motion than did patients presenting with tighter stenosis and no collaterals; this suggests that early reperfusion either by anterograde recanalization or through collaterals could limit infarct size. Because the prevalence of well-developed collaterals was similar in transmural and nontransmural MI, the factors responsible for the smaller infarct size in the latter appear to be either a

lower prevalence of total or subtotal occlusion or involvement of smaller branches.

Prognosis: Multivariate analysis[15–19,31–33] identified left ventricular ejection fraction, the number of narrowed arteries, severe congestive heart failure in the acute phase, and a previous history of MI as the main determinants of prognosis in patients with coronary artery disease. Series analyzing long-term survival after nontransmural infarction[4–10] are heterogeneous as they include patients with wide differences in age, degree of left ventricular dysfunction, and prevalence of previous MI. The present report is the first prospective study on the long-term prognosis of patients surviving first nontransmural MI that includes angiographic information. This group of patients had better left ventricular function and a higher prevalence of either nonobstructive coronary artery disease or distally located obstructive lesions than did those presenting with transmural involvement.

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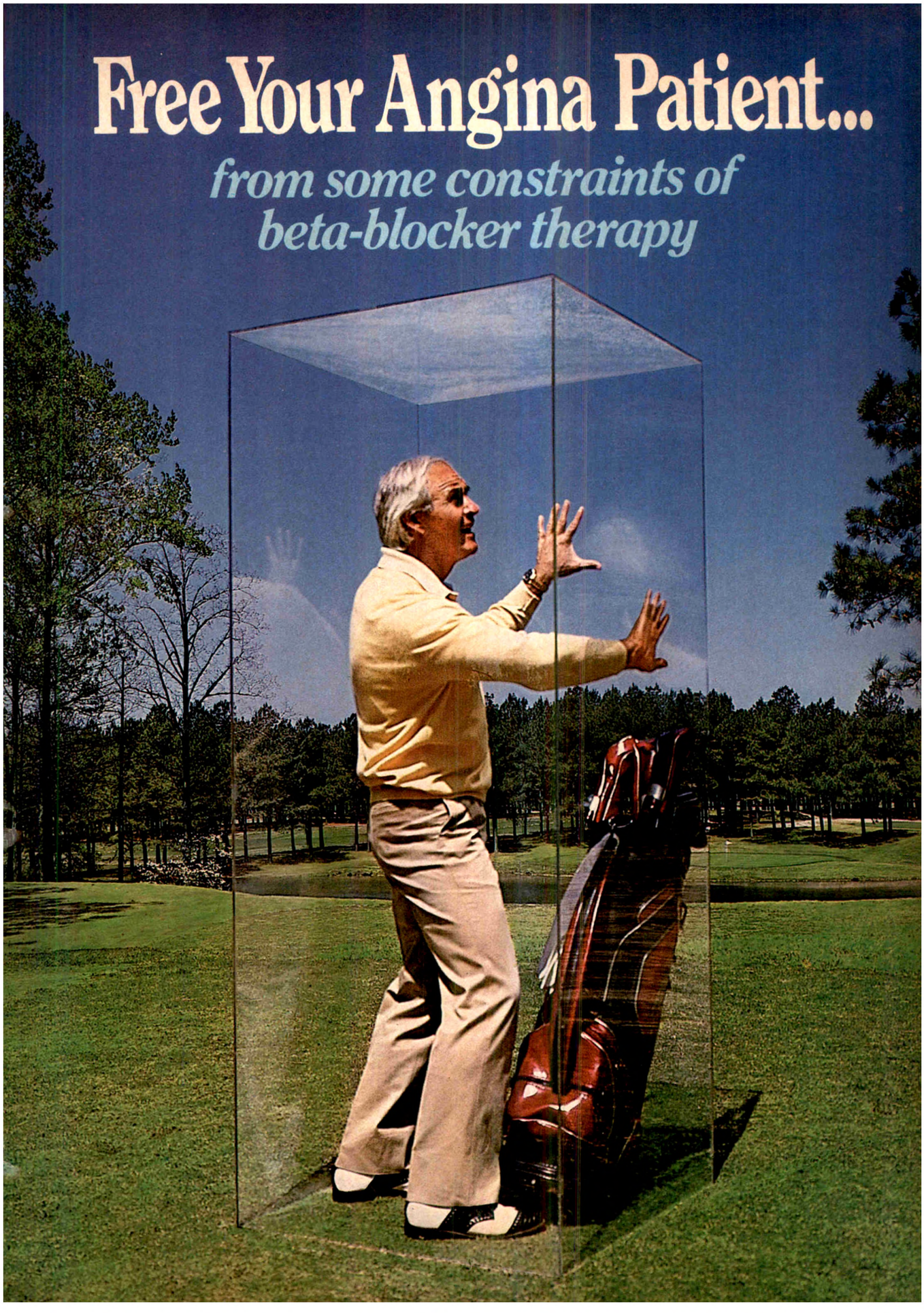
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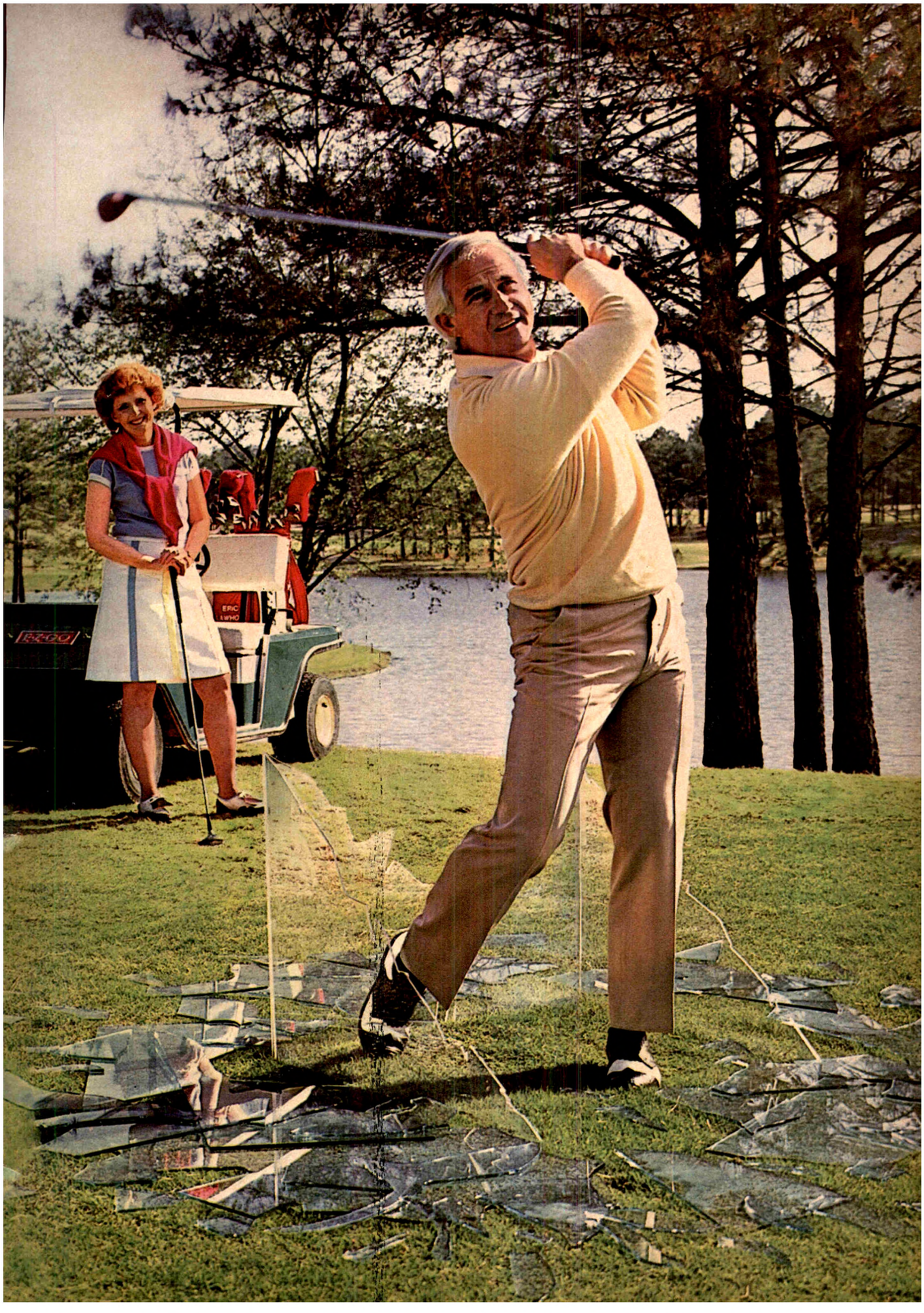
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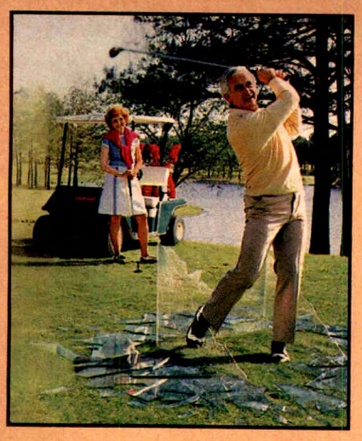

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Symptomatic, Electrocardiographic, Metabolic, and Hemodynamic Alterations During Pacing-Induced Myocardial Ischemia

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Atrial pacing has been used to assess the physiologic impact of coronary artery disease (CAD). Several variables have served as markers of pacing-induced myocardial ischemia, but their specificities and sensitivities are unknown. Accordingly, in 28 patients, incremental atrial pacing was performed. Of the 28, 10 had no CAD. The left ventricular ejection fraction (LVEF) (by gated equilibrium blood pool scintigraphy) increased in this group (0.60 ± 0.11 [mean ± standard deviation] before pacing to 0.67 ± 0.13 at peak-pacing, p = 0.002). In no patient did left ventricular end-diastolic pressure increase by >5 mm Hg. No patient had lactate production, and 2 (20%) had electrocardiographic S-T segment depression ≥0.1 mV. Four (40%) had chest pain with atrial pacing. In the remaining 18 patients with CAD, atrial pacing caused a decrease in LVEF ≥0.05 (0.46 ± 0.10 to 0.33 ± 0.09, p <0.001) and new segmental wall motion abnormalities in all, indicating pacing-induced myocardial ischemia. Only 8 (44%) had an increase in left ventricular end-diastolic pressure of >5 mm Hg, and only 9 (50%) had lactate production. Ten (56%) had ischemic electrocardiographic changes, and 12 (67%) had chest pain. Thus, the electrocardiographic, metabolic, and hemodynamic alterations that may accompany pacing-induced ischemia are specific but relatively insensitive markers of ischemia. In contrast, chest pain during atrial pacing is a nonspecific occurrence, appearing with similar frequency in normal subjects and patients with CAD and pacing-induced ischemia.

Rapid atrial pacing has been used in the catheterization laboratory as a controlled and reproducible method of producing myocardial ischemia in patients with underlying coronary artery disease (CAD).[1–3] In these individuals, pacing has been shown to induce angina-like chest pain,[4–9] electrocardiographic S-T segment depression,[4–7,9–11] myocardial lactate production,[4,11–14] and increases in left ventricular (LV) filling pressure.[4,10,11,15–18] However, the frequency with which each of these variables occurs in patients with pacing-induced ischemia varies substantially among these reports. In addition, few studies have examined these variables in persons without CAD. Therefore, this study examines the sensitivities and specificities of the symptomatic, electrocardiographic, metabolic, and hemodynamic alterations caused by rapid atrial pacing.

From the Department of Internal Medicine (Cardiovascular Division) and Radiology (Nuclear Medicine), the University of Texas Health Science Center, Dallas, Texas. This study was supported in part by Ischemic SCOR Grant HL 17669 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and the Harry S. Moss Heart Fund, Dallas, Texas. Manuscript received December 7, 1982; revised manuscript received February 14, 1983, accepted February 15, 1983.

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Methods

Patient population: The study was performed in 41 persons (28 men, 13 women, mean age 53 years) without valvular, congenital, pericardial, or primary myocardial disease referred for catheterization for the evaluation of chest pain. All patients were in sinus rhythm and had normal ventricular activation. No cardiac medications were administered within 8 hours of the study. In all patients, the entire protocol was performed before the introduction of radiographic contrast material. Based on the results of coronary arteriography and pacing-induced alterations in the left ventricular ejection fraction (LVEF), the patients were assigned to 1 of 3 groups.

Control group: Ten persons (5 men, 5 women, mean age 51 years) had no angiographic evidence of CAD. At the time of catheterization, all 10 were taking oral isosorbide dinitrate,

2 were taking propranolol, 2 were receiving nifedipine, and 1 was receiving digoxin.

Ischemic group: In 18 patients (13 men, 5 women, mean age 54 years) with CAD (defined as ≥70% luminal diameter narrowing of 1 or more major epicardial coronary arteries), myocardial ischemia was induced by rapid atrial pacing, as evidenced by a decrease in LVEF of ≥0.05 and new segmental wall motion abnormalities, both assessed by equilibrium gated blood pool scintigraphy. Of these 18, 11 were taking long-acting nitrates, 10 were receiving propranolol, 4 were receiving nifedipine, and 4 were taking digoxin.

Nonischemic group: In 13 patients (10 men, 3 women, mean age 53 years) with CAD, rapid atrial pacing did not induce a decrease in LVEF of ≥0.05 or segmental wall motion abnormalities. Since these persons did not have pacing-induced ischemia, they were excluded from further analysis.

Study protocol: In each patient, a 7 or 8Fr Gorlin catheter was advanced from the right basilic vein to a position approximately 2 cm into the coronary sinus; its location was confirmed fluoroscopically and oximetrically. A 9Fr polyurethane sheath was introduced percutaneously into the femoral artery, and its side-arm was connected to a pressure transducer for the monitoring of femoral arterial pressure and the acquisition of blood samples. Through this sheath, an 8Fr micromanometer-tipped pigtail catheter (Millar Instruments, Houston, Texas) was advanced to the left ventricle. Before pacing, arterial and coronary sinus blood samples were obtained for quantitation of lactate and oxygen content. In addition, a 12-lead electrocardiogram, a radionuclide ventriculogram, heart rate, femoral arterial pressure, and LV end-diastolic pressure were recorded. Subsequently, continuous atrial pacing was begun at 100 beats/min and increased every 4 minutes by 20 beats/min until chest pain or atrioventricular block occurred or until a heart rate of 140 beats/min was achieved. After 1 minute at the peak pacing rate, acquisition of another radionuclide ventriculogram was initiated. During the 15 seconds before the termination of pacing, arterial and coronary sinus blood samples again were obtained for measurement of lactate and oxygen content, and a 12-lead electrocardiogram was recorded during the 10 seconds after pacing was discontinued. LV end-diastolic pressure was recorded for 30 seconds after the abrupt termination of pacing.

Electrocardiographic and metabolic assessments: Ischemic electrocardiographic alterations were defined as at least 1 mm (0.1 mV) of horizontal or downsloping S-T segment depression 0.08 second after the J point in comparison to the baseline tracing.[19] Blood samples for lactate determination were immediately deproteinated in iced perchloric acid, centrifuged, decanted, and stored frozen. Lactate concentrations were assayed enzymatically with a commercial kit (Sigma Chemical, St Louis, Missouri). For each pair of blood samples, the percent myocardial lactate extraction was calculated using the formula $100 \times (A\text{-}CS)/A$, where A represents the arterial lactate concentration and CS the coronary sinus lactate concentration. Using this formula, a value less than zero is indicative of myocardial lactate production.[20] Finally, arterial and coronary sinus oxygen contents were determined with a Lex-O_2-Con analyzer (Lexington Instruments, Lexington, Massachusetts). These data were used to confirm that the coronary sinus catheter had not become inadvertently dislodged during rapid atrial pacing.

Hemodynamic assessments: Before pacing, LV end-diastolic pressure was measured coincident with the peak of the electrocardiographic R-wave; in each patient, 10 consecutive beats were averaged. To obtain the postpacing end-diastolic pressure, 10 consecutive beats again were averaged, beginning with the sixth beat after pacing was abruptly discontinued, as previously described.[21] For the purposes of this study, an increase in LV end-diastolic pressure from before to immediately after pacing of >5 mm Hg was considered abnormal.[10]

Radionuclide ventriculography: Red blood cells were labeled with radioisotope using a technique combining features of in vitro and in vivo labeling.[22] Scintigraphic data collection was performed with a portable gamma scintillation camera (Series Sigma 420, Ohio Nuclear, Solon, Ohio) equipped with an all-purpose parallel hole collimator and interfaced with a dedicated on-line computer system (Series 550). Equilibrium gated blood pool scintigrams were obtained in a modified left anterior oblique projection adjusted to allow the clearest septal visualization and left ventricular isolation. All studies were gated for 32 frames per cardiac cycle and collected for 100% of the cardiac cycle. The scintigraphic images were acquired for a predetermined number of cardiac cycles so that the total acquisition time of the study was 3 minutes. This procedure resulted in a minimum of 100,000 counts per frame of the study. All data were stored on magnetic disks for subsequent analysis.

LVEF was determined from the time-activity LV curve by constructing a region of interest over the left ventricle in the end-diastolic (ED) and end-systolic (ES) frames. After correcting for background activity, LVEF was calculated using the formula: LVEF = (ED counts − ES counts)/ED counts. This method has been shown to correlate well with results obtained by contrast angiography.[23] In this study, a decrease in LVEF of ≥0.05 (the accepted limit of observer error)[24] was considered abnormal.

A subjective analysis of regional wall motion also was performed. The image border in the left anterior oblique projection was divided into 5 equal segments identified as the basal-lateral, apical-lateral, apical, apical-septal, and basal-septal.[25] Wall motion was graded according to the following scale: 3 = normokinesia, 2 = mild hypokinesia, 1 = severe hypokinesia, 0 = akinesia, and −1 = dyskinesia. Changes in wall motion of 1 or more units were considered abnormal.

Statistical analysis: All results are reported as mean ± 1 standard deviation. For the analysis of the heart rate-systolic arterial pressure "double product," LVEF, and end-diastolic pressure within each group of patients, baseline values were compared with peak or after pacing values with a paired *t* test. For the comparison of these values between groups, an unpaired *t* test was employed. The change in LV end-diastolic pressure induced by pacing was compared with the pacing-induced alteration of LVEF by a 2-variable linear regression analysis. Finally, the sensitivities and specificities of each variable in each of the 2 patient groups were compared with a chi-square analysis.[26,27] For all analyses, a p value <0.05 was considered significant.

Results

Control group (n = 10) (Table I): In those without CAD, double product (heart rate × systolic arterial pressure) was 10.1 ± 2.4 × 10^3 units at rest and increased to 18.5 ± 2.1 × 10^3 units at peak pacing ($p < 0.001$). Pacing was accomplished at 140 beats/min in 8 of the 10 persons; in the remaining 2, it could not be performed above 120 beats/min because of atrioventricular block. Resting LVEF averaged 0.60 ± 0.11. At peak-pacing, it increased to 0.67 ± 0.13 ($p = 0.002$), and no patient had regional wall motion abnormalities. Of the 10 patients, 4 had their usual chest pain at peak-pacing, 2 had S-T segment alterations compatible with ischemia, and none had myocardial lactate production or an increase in LV end-diastolic pressure >5 mm Hg.

TABLE I Symptomatic, Electrocardiographic, Metabolic, and Hemodynamic Responses to Rapid Atrial Pacing in Patients With Normal Coronary Arteries (Control Group)

Patient	Age (yr) & Sex	Peak Pacing HR (beats/min)	Double Product × 10^3 Units		Chest Pain	S-T Depression	LVEDP (mm Hg)		LVEF	
			Pre	Peak			Pre	Post	Pre	Peak
1	42M	120	6	17	0	0	17	18	0.61	0.71
2	35M	140	9	15	0	0	12	12	0.59	0.71
3	58F	140	10	20	+	+	11	12	0.62	0.66
4	62M	120	11	21	+	0	17	15	0.53	0.63
5	43M	140	9	18	+	0	17	19	0.54	0.56
6	69F	140	15	22	+	0	21	23	0.48	0.55
7	49M	140	10	18	0	0	17	16	0.81	0.92
8	56F	140	13	19	0	0	5	7	0.75	0.81
9	49F	140	8	18	0	+	17	20	0.48	0.50
10	42F	140	11	17	0	0	17	15	0.62	0.61
Mean 51		...	10 ± 2	19 ± 2	...	...	15.1 ± 4.5	15.7 ± 4.6	0.60 ± 0.11	0.67 ± 0.13
SD		...	...	...	...	...				
			p <0.001				NS		p = 0.002	

HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; SD = standard deviation.

For the 10 patients, left ventricular end-diastolic pressure averaged 15.1 ± 4.5 mm Hg at baseline and 15.7 ± 4.6 mm Hg immediately after pacing (not significant).

Ischemic group (n = 18) (Table II): All patients had angiographic evidence of CAD (1-vessel in 5, 2-vessel in 7, and 3-vessel in 6). At rest, double product was 9.0 ± 2.3 × 10^3 units, increasing to 17.8 ± 4.8 × 10^3 units at peak pacing ($p < 0.001$). The resting LVEF was 0.46 ± 0.10. With pacing, it decreased by ≥0.05 in all patients, so that at peak pacing it was 0.33 ± 0.09 ($p < 0.001$). All 18 had new wall motion abnormalities at peak-pacing. Of the 18 patients, 12 (67%) had their usual chest discomfort, 10 (56%) had postpacing S-T segment depression, 9 (50%) had myocardial lactate production, and 8 (44%) had an increase in LV end-diastolic pressure of >5 mm Hg. There was no correlation between the increase in end-diastolic pressure and the decrease in LVEF with pacing (r = 0.13, Fig. 1).

Of the 18 patients with CAD and pacing-induced LV dysfunction, 13 had a decrease in LVEF of ≥0.10. Of these 13 persons with an especially prominent pacing-induced functional change, 10 (77%) had chest discomfort, 7 (54%) had postpacing S-T segment depression ≥0.1 mV, 7 (54%) had myocardial lactate production, and 7 (54%) had an increase in LV end-diastolic pressure of >5 mm Hg. No variable occurred more frequently in these 13 patients than in the entire group of 18.

Finally, 8 of the 18 patients with CAD and pacing-induced LV dysfunction had a LVEF ≥0.50 during the baseline study, whereas the resting ejection fraction in the remaining 10 was <0.50. Of these 8 patients, 6 (75%) had pacing-induced chest pain, 6 (75%) had ischemic S-T segment alterations, 5 (63%) had lactate production, and 5 (63%) had a substantial (>5 mm Hg) increase in postpacing LV end-diastolic pressure. Ten of the 18 individuals with CAD and a pacing-induced decrease in the LVEF had a prepacing LV end-diastolic pressure ≤16 mm Hg. Of these, 6 (60%) had pacing-induced chest pain, 5 (50%) had ischemic S-T segment depression, and 4 (40%) had myocardial lactate production.

Discussion

Previous studies have demonstrated that rapid atrial pacing may induce chest pain,[4–9] electrocardiographic S-T segment depression,[4–7,9–11] myocardial lactate production,[4,11–14] and an increase in LV end-diastolic pressure[4,10,11,15–18] in persons with CAD, but the relative sensitivities and specificities of these variables have not been assessed. Therefore, this study was performed to examine each of these variables in normal subjects (persons with chest pain and angiographically normal coronary arteries) and those with pacing-induced ischemia, as reflected by a deterioration in LVEF and the appearance of new segmental wall motion abnormalities. The data provided in this study indicate that postpacing S-T segment depression, peak-pacing

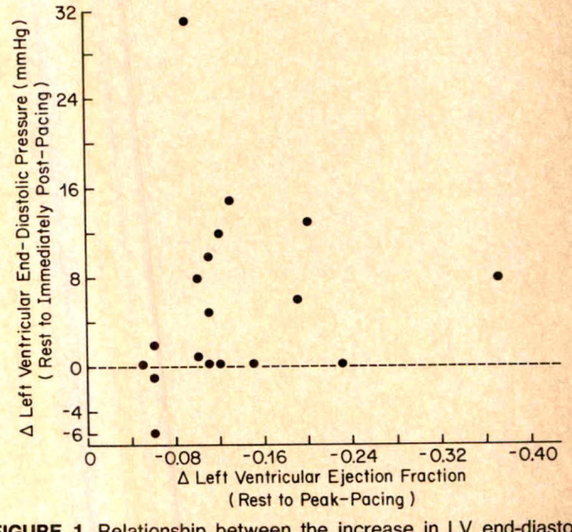

FIGURE 1. Relationship between the increase in LV end-diastolic pressure (in mm Hg) from rest to postpacing (**vertical axis**) and the decrease in LVEF from rest to peak-pacing (**horizontal axis**) for the 18 patients with CAD and pacing-induced ischemia. Each dot represents the data from 1 patient. There is no correlation between these 2 variables (r = 0.13, p = 0.60).

TABLE II Symptomatic, Electrocardiographic, Metabolic, and Hemodynamic Responses to Rapid Atrial Pacing in Patients With Coronary Artery Disease and Pacing-Induced Left Ventricular Systolic Dysfunction (Ischemic Group)

Pt	Age (yr) & Sex	Peak Pacing HR (beats/min)	Double Product × 10^3 Units		Chest Pain	S-T Depression	Lactate Production	LVEDP (mm Hg)		LVEF		Percent Diameter Narrowing of Coronary Arteries		
			Pre	Peak				Pre	Post	Pre	Peak	LAD	LC	Right
1	50M	140	8	19	+	0	+	17	29	0.40	0.28	100	90	50
2	51M	120	7	15	+	+	0	15	15	0.46	0.41	75	0	100
3	45M	140	8	16	+	+	+	16	22	0.61	0.42	99	99	99
4	59M	140	10	26	+	+	0	15	30	0.35	0.22	100	75	0
5	64F	120	9	12	+	+	+	21	21	0.50	0.27	99	90	99
6	60M	140	9	14	+	+	+	26	26	0.25	0.14	50	99	100
7	61M	140	8	15	0	0	0	17	11	0.40	0.34	75	0	100
8	50M	140	7	18	+	0	+	16	17	0.42	0.32	100	0	0
9	52F	120	8	11	0	0	0	16	16	0.38	0.26	100	0	0
10	52M	120	9	17	+	+	0	14	24	0.41	0.30	100	100	0
11	50F	140	10	26	+	+	+	11	42	0.50	0.41	99	90	100
12	42M	140	10	19	0	+	+	21	23	0.50	0.44	100	0	0
13	60M	140	8	15	0	0	+	14	19	0.37	0.26	100	0	50
14	46M	120	8	14	0	0	0	10	10	0.45	0.30	99	100	100
15	47M	140	7	22	+	+	0	17	25	0.68	0.31	90	left main	90
16	72M	120	14	23	+	0	+	27	35	0.57	0.47	90	99	0
17	40F	140	6	13	0	0	0	10	9	0.50	0.44	99	0	0
18	63F	140	14	26	+	+	0	21	34	0.56	0.36	99	90	90
Mean 54		...	9 ± 2	18 ± 5	...	...	...	...	...	0.46 ±	0.33 ±	...	...	...
SD		...	...	...	...	...	...	...	...	0.10	0.09	...	...	...
			p <0.001							p <0.001				

LAD = left anterior descending; LC = left circumflex; Pt = patient; other abbreviations as in Table I.

myocardial lactate production, and postpacing increases in LV end-diastolic pressure are specific but relatively insensitive markers of pacing-induced ischemia. At the same time, pacing-induced chest pain is a relatively nonspecific occurrence, appearing with similar frequency in normal persons and those with underlying CAD and pacing-induced ischemia.

Pacing-induced chest pain: Several studies have indicated that pacing-induced chest pain is a highly sensitive and specific marker for underlying CAD.[4–9] In fact, in some studies[4,10,11,15–18] chest discomfort has served as the variable to which all other (such as lactate production and increases in LV end-diastolic pressure) are compared. In our experience, however, chest pain during pacing is an unreliable reflector of ischemia, since some patients cannot differentiate between ischemic chest pain and the palpitations associated with atrial pacing. Indeed, in the present study, 4 (40%) of the 10 patients without CAD or scintigraphic evidence of ischemia had their usual chest pain during pacing.

Pacing-induced electrocardiographic S-T segment depression: Although some studies[5] have demonstrated an excellent relationship between pacing-induced chest pain and S-T segment depression *during* pacing, others[9] have shown that S-T depression during pacing is neither specific nor sensitive in the identification of persons with CAD. Since rapid atrial pacing, in itself, produces certain electrocardiographic abnormalities,[4,21] we assessed pacing-induced S-T segment alterations in the immediate *postpacing* period. Ten (56%) of the 18 patients with pacing-induced ischemia had ≥0.1 mV of S-T segment depression on the postpacing electrocardiogram, but 2 (20%) of the 10 normal subjects also had such S-T segment alterations. Thus, postpacing electrocardiographic S-T segment depression offers only modest specificity and sensitivity in the identification of pacing-induced ischemia.

Pacing-induced myocardial lactate production: Pacing-induced myocardial ischemia leads to anaerobic glycolysis in the ischemic tissue, resulting in the release of lactate into the coronary venous effluent.[4,12–14,28–30] At the same time, the systemic arterial lactate concentration is stable. Thus, the normally oxygenated and perfused myocardium extracts lactate, whereas the ischemic myocardium produces it. Previous studies[4,10,11,14] have shown that lactate production occurs in most patients with CAD during pacing-induced angina. Our data indicate that myocardial lactate production is specific for pacing-induced ischemia, in that none of the 10 normal subjects produced lactate during pacing. However, lactate production is not a sensitive marker of pacing-induced ischemia: of the 18 patients with pacing-induced LV dysfunction, only 9 (50%) had lactate production. Our data show no relationship between lactate production and the severity of pacing-induced LV dysfunction. The 9 patients with lactate production had a pacing-induced decrease in the LVEF of 0.12 ± 0.05, whereas the 9 persons without lactate production had an average decrease of 0.14 ± 0.10 (not significant in comparison to the 9 who produced lactate). It is conceivable that lactate production is not demonstrable in some patients during pacing-induced ischemia because (1) coronary sinus blood sampling is not performed at the precise time of greatest lactate efflux, or (2) the lactate produced by ischemic tissue is diluted in the coronary venous effluent by drainage from nonischemic areas.

Pacing-induced increases in LV filling pressure: An elevated LV end-diastolic pressure is a common occurrence during angina in patients with CAD.[2,5,15,31,32] When angina is induced by atrial pacing, LV end-diastolic pressure usually increases with the onset of angina and becomes maximally elevated in the immediate postpacing period.[4,10,11,15–18] Although several studies have assessed postpacing alterations in LV end-diastolic pressure in patients with CAD, there is disagreement as to the frequency with which such elevations occur.[10,16–18] As with the production of lactate, our data indicate that a substantial (>5 mm Hg) increase in postpacing LV end-diastolic pressure is a specific but relatively insensitive marker of pacing-induced ischemia. Such elevations did not occur in the 10 normal subjects, but they occurred in only 8 (44%) of the 18 with pacing-induced LV systolic dysfunction. Furthermore, although McKay et al[33] have demonstrated a good correlation between pacing-induced hemodynamic changes and LV segmental hypoperfusion (as assessed by thallium scintigraphy), our data show no relationship between the magnitude of change in LV end-diastolic pressure and that in LVEF with pacing (Fig. 1).

Use of alterations in LVEF and segmental wall motion as indexes of pacing-induced myocardial ischemia: In the present study we used a decrease in LVEF of ≥0.05 and the appearance of new segmental wall motion abnormalities during pacing as indicators of myocardial ischemia. The use of these functional markers is supported by numerous studies in experimental animals and man showing that ischemia impairs LV systolic performance.[34–40] In each patient with CAD, a decrease in LVEF of ≥0.05 from rest to peak-pacing was required, since Wackers et al[24] have shown that alterations in LVEF of smaller magnitude are within the accepted limits of observer variability with multigated equilibrium blood pool imaging.

Clinical implications: Although selective coronary arteriography allows identification of obstructive CAD, it gives no information about the physiologic importance of such disease. In most patients, this information can be obtained by exercise testing or atrial pacing at the time of cardiac catheterization. Previous studies have suggested that pacing-induced chest pain, electrocardiographic alterations, lactate production, and elevations of LV end-diastolic pressure are reliable markers of ischemia, but their sensitivities and specificities are unknown. The present study demonstrates (1) that chest pain during atrial pacing is a nonspecific occurrence, since it appears with similar frequency in normal persons (40%) and those with CAD and pacing-induced ischemia (67%) (not significant); (2) that postpacing electrocardiographic S-T segment depression ≥0.1 mV occurs in slightly more than half those with pacing-induced ischemia, but it also occurs on occasion in normal persons; and (3) and that both peak-pacing myocardial lactate production and post-

pacing elevations of LV end-diastolic pressure are highly specific but relatively insensitive reflectors of pacing-induced ischemia. It is possible that this relative insensitivity might improve if atrial pacing were performed more rapidly (>140 beats/min) or for a longer period of time (>4 minutes).

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Effect of Oral Sustained-Release Nitroglycerin on Exercise Capacity in Angina Pectoris: Dose-Response Relation and Duration of Action During Double-Blind Crossover Randomized Acute Therapy

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Ten men with documented coronary artery disease and stable exertional angina underwent a double-blind crossover study to examine the benefit and the duration of action on their symptom-limited exercise capacity of 2 doses (2.5 and 6.5 mg) of sustained-release nitroglycerin (SRNG). A multistage bicycle test was performed in the sitting position by steps of 30 W each 3 minutes until the onset of typical angina pectoris. It was performed 24 hours before the start of the study; 1 and 5 hours after administration of placebo, and repeated after 2.5 and 6.5 mg of SRNG administered in a double-blind crossover study according to a 4 successive days protocol. No differences appeared between administration of placebo (1 and 5 hours) and the results obtained at the first exercise test. The dose of 2.5 mg of SRNG was effective on the symptom-limited working capacity but only at 1 hour (+9%; $p < 0.01$). The dose of 6.5 mg was more effective both at 1 hour (+25%; $p < 0.001$) and at 5 hours (+27%; $p < 0.001$). All patients had angina at a higher heart rate (+5 to 8%; p = NS [not significant] and $p < 0.01$), whereas systolic blood pressure and double product tended to be slightly but insignificantly increased. S-T depression at the onset of angina was insignificantly changed with placebo, and 2.5 and 6.5 mg of SRNG. It is concluded that 6.5 mg of orally administered SRNG is effective during at least 5 hours, and that the magnitude of the benefit and its duration are dose-related.

Because the duration of action on sublingual nitroglycerin is relatively short, there has been a search for a pharmacologic agent that would have prolonged therapeutic effectiveness. Three basic approaches to a prolonged pharmacologic action of nitroglycerin have been evaluated by utilizing an ointment base, an organic nitrate compound (isosorbide dinitrate and pentaerythritol tetranitrate), and the formulation of timed disintegration granules with controlled and sustained release of a therapeutic dose of nitroglycerin. The investigation reported here evaluated the therapeutic effectiveness of 2 doses, 2.5 and 6.5 mg of a sustained-release nitroglycerin preparation (SRNG) (Nysconitrine®, 2.5 and 6.5 mg) orally administered to patients with angina pectoris. The efficacy of both dosages was evaluated in a double-blind crossover investigation of the SRNG preparation compared with an identically presenting placebo capsule, according to objective criteria (that is, symptom-limited maximal working capacity measured during a graded exercise test).

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Methods

Patient group: Ten men, aged 48 to 70 years (mean, 61 ± 8) with stable grade II exertional angina pectoris were studied. Patients with symptoms or clinical evidence of congestive heart failure were excluded. During the study period, no other treatment (beta-blocking agents or calcium-channel inhibitors) was allowed.

The diagnosis of coronary artery disease was based on both a positive coronary angiogram (≥50% reduction in luminal diameter of at least 1 coronary artery) and a positive exercise thallium scan. Five patients had 1-vessel disease, 3 patients

TABLE I Comparison Between Maximal Values Obtained Before the Study and Under Placebo Conditions

		D (min)	HR (beats·min^{-1})	SBP (mm Hg)	PRP (mm Hg beats·min^{-1})	S-T↓ (mm)
BET	Mean ± SD	8.0 ± 2.9	117 ± 16	184 ± 20	21,528 ± 4,600	1.6 ± 0.7
Placebo (1 hour)	Mean ± SD	8.0 ± 2.9	116 ± 15	186 + 22	21,672 ± 4,508	1.5 ± 0.6
Placebo (5 hour)	Mean ± SD	7.9 ± 2.9	121 ± 19	182 ± 18	22,147 ± 4,836	1.7 ± 0.9
BET vs placebo (1 hour)	Val	0	−1.1	+2.0	+144	−0.1
	Δ%	0	−0.9	+1.0	+0.6	−6.2
	p	NS	NS	NS	NS	NS
BET vs placebo (1 hour)	Val	−0.1	+4	−2	+619	+0.1
	Δ%	−1.0	+3.3	−1.0	+2.8	+6.2
	p	NS	NS	NS	NS	NS
Placebo (1 hour) vs placebo (5 hours)	Val	−0.1	+5.1	−4.0	+47.5	+0.2
	Δ%	−1.0	+4.3	−2.0	+2.1	+12
	p	NS	NS	NS	NS	NS

BET = basic exercise test; D = maximal working capacity expressed in duration; HR = maximal heart rate; NS = not significant; p = probability; PRP = maximal pressure-rate product; SD = standard deviation; SPB = maximal systolic blood pressure; S-T↓ = maximal S-T segment depression; Val = absolute value; Δ = difference.

had 2-vessel disease and 2 patients 3-vessel disease. No patient had S-T segment depression on the resting electrocardiogram, but all had angina pectoris and S-T segment depression during exercise. No complications occurred as a result of the experimental procedure.

Protocol: The patients first performed a multistage bicycle exercise test in the sitting position: After an initial work load of 30 W during 3 minutes, the load was increased by 30 W every 3 minutes. Exercise was continued until the onset of typical angina pectoris. A 12-lead electrocardiogram was recorded every minute. Electrocardiographic leads V_3, V_4, V_5, and V_6 were continuously monitored on an oscilloscope. Lead V_5 was automatically analyzed. An exercise test was considered positive when the surface limited by the resting S-T level and the depressed S-T segment, 0.02 to 0.08 second from the top of the R wave, was ≥7.5 mV·s. All patients had a positive exercise test according to these criteria.

Twenty-four, 48, and 72 hours later, the same multistage graded exercise was performed 1 and 5 hours after administration of placebo and 2.5 or 6.5 mg of SRNG preparation, administered according to a double-blind crossover randomized protocol. Symptom-limited working capacity was expressed as the duration of the standardized exercise test. The experiments took place in an air conditioned room (temperature, 20°C to 23°C; humidity, 40 to 60%), all patients having already performed at least 1 exercise test before the present procedure. The following variables were measured or calculated: (1) maximal symptom-limited working capacity, expressed in minutes of duration of the progressive exercise test; (2) maximal heart rate; (3) maximal systolic blood pressure; (4) S-T segment depression in mm; and (5) double product (heart rate × systolic blood pressure).

Statistical analysis was performed by Student's paired *t* test.

Results

The various parameters, measured 1 and 5 hours after placebo administration, did not differ significantly from values measured during the basic exercise test (Table I). The mean values for symptom-limited maximal exercise capacity comparing placebo and SRNG (2.5 and 6.5 mg) are presented in Table II.

Symptom-limited maximal working capacity measured 1 hour after administration of 2.5 mg of SRNG compared with that 1 hour after placebo administration increased by 9% ($p < 0.01$), heart rate by 5% (NS), systolic blood pressure by 8% ($p < 0.05$), double product by 12% (NS), and S-T segment depression by 8% (NS).

Symptom-limited maximal working capacity measured 5 hours after administration of 2.5 mg of SRNG compared with that 5 hours after placebo administration remained unchanged (+1%; NS), heart rate increased by 2% (NS), systolic blood pressure by 6% ($p < 0.05$), double product by 7% (NS), and S-T segment depression was unchanged (−2%; NS).

Symptom-limited maximal working capacity measured 1 hour after administration of 6.5 mg of SRNG compared with that 1 hour after placebo administration improved by 25% ($p < 0.001$), heart rate increased by 8% ($p < 0.01$), systolic blood pressure was unchanged (+1%; NS), double product increased by 10% (NS), and S-T segment by 7% (NS).

Symptom-limited maximal working capacity measured 5 hours after administration of 6.5 mg of SRNG compared with that 5 hours after placebo administration remained significantly improved (+27%; $p < 0.001$). Heart rate increased by 5% (NS) and systolic blood pressure by 4% (NS). The double product was significantly higher (+8%; $p < 0.01$), whereas the S-T segment depression remained unchanged (+1%; NS).

Discussion

Our results demonstrate that orally administered SRNG was rapidly absorbed from the gastrointestinal tract and exerted an antianginal effect 1 hour after intake. The drug produced a dose-related increase in symptom-limited maximal working capacity (+9% and 25%, 1 hour after 2.5 and 6.5 mg of SRNG, respectively). We could also demonstrate a dose-related increase in the duration of action: Maximal symptom-limited exercise capacity was unaffected 5 hours after administration of 2.5 mg of SRNG, whereas a 27% increase was still present 5 hours after administration of 6.5 mg. The study involved 7 repeated exercise tests over 4 days. A training effect could have influenced the exercise performance of the patients. This was taken into account in designing the study: Each patient was studied after a double-blind crossover administration of placebo, and

TABLE II Maximal Values 1 and 5 Hours After Placebo or 2.5 or 6.5 mg of Sustained-Release Nitroglycerin (SRNG)

		1 Hour				5 Hours				
	D (min)	HR (beats·min^{-1})	SBP (mm Hg)	PRP (mm Hg·min^{-1})	S-T↓ (mm)	D (min)	HR (beats·min^{-1})	SBP (mm Hg)	PRP (mm Hg·min^{-1})	S-T↓ (mm)
Placebo (Mean ± SD)	8.0 ±2.9	116 ±15	186 ±22	21,672 ±4,508	1.5 ±0.6	7.9 ± 2.9	121 ±19	182 ±18	22,147 ±4,836	1.7 ±0.9
SRNG (2.5 mg) (Mean ± SD)	8.7 ±2.4	121 ±17	201 ±22	24,295 ±3,714	1.7 ±0.6	8.0 ±2.9	124 ± 22	193 ±18	23,739 ±3,977	1.7 ±0.9
SRNG (6.5 mg) (Mean ± SD)	10.0 ±2.9	126 ±21	188 ±25	23,820 ±5,751	1.7 ±0.8	10 ±3	127 ±21	189 ±22	23,923 ±4,751	1.7 ±1.1
SRNG (2.5 mg vs Placebo)	Val +0.7	+5.4	+15.0	+2,623	+0.13	+0.1	+2.7	+110	+1,592	−0.03
	Δ% +9%	+5%	+8%	+12%	+8%	+1%	+2%	+6%	+7%	−2%
	p <0.01	NS	<0.05	NS	NS	NS	NS	<0.05	NS	NS
SRNG (6.5 mg vs Placebo)	Δ% +2.0	+9.7	+2.0	+2,148	+0.11	+2.1	+5.6	+7	+1,776	+0.01
	+25%	+8%	+1%	+10%	+7%	+27%	+5%	+4%	+8%	+1%
	p <0.001	<0.01	NS	NS	NS	<0.001	NS	NS	<0.01	NS
SRNG (6.5 vs 2.5 mg)	Val +1.3	+4.3	−13.0	−475	−0.2	+2.0	+2.9	−40	+184	+0.4
	Δ% +15%	+4%	−6%	−2%	−1%	+25%	+2%	−2%	+1%	+2%
	p <0.01	NS	NS	NS	NS	<0.01	NS	NS	NS	NS

Abbreviations as in Table I.

2.5 or 6.5 mg of SRNG. No statistically significant differences were observed between the basic exercise test values and the values observed during the tests performed on the first, second, or third day under placebo conditions.

Although sublingual nitroglycerin prolongs exercise tolerance in patients with angina pectoris,[1–4] the usefulness of SRNG or long-acting nitrates in angina pectoris was seriously questioned until recently.[5] The reasons for conflicting opinions about long-acting nitrates are varied: (1) Poor to no statistical method. When considering properly designed investigations, long-acting nitrates are usually found to be ineffective.[6] (2) The major difficulty in designing adequate clinical evaluations of antianginal therapy.[5,7,8] (3) The works of Needleman and Johnson[9] showing that orally administered nitrates are rapidly metabolized in the liver, allowing little or none of the active molecule to reach the systemic circulation. However, more recently, several well-designed studies have shown prolonged effects of long-acting nitrates in increasing exercise tolerance in patients with angina.[8,10,11] Three long-acting nitrate formulations have shown clear-cut effectiveness in recent studies: isosorbide dinitrate, oral sustained-action nitroglycerin, and nitroglycerin ointment.[12]

As far as SRNG is concerned, only 2 well-designed contemporary studies reported a sustained efficacy in patients with angina: Improved exercise tolerance was shown up to 4 hours after the last oral dose of 6.5 mg of nitroglycerin.[8,11]

In the present investigation, we evaluated the duration of action as well as the influence on symptom-limited exercise capacity and other exercise parameters of an orally administered SRNG at 2 different doses: 2.5 and 6.5 mg, administered randomly and in double-blind manner, compared with placebo. The 2.5 mg dose increased exercise duration by 9% at 1 hour, but was ineffective at 5 hours. In contrast, 6.5 mg of SNRG increased exercise capacity by 25% for 5 hours. All patients were stopped by angina at a higher level of heart rate (5 to 8%), whereas systolic blood pressure and double product tended to be slightly but insignificantly increased. However, double product was significantly increased 5 hours after administration of 6.5 mg of SRNG. S-T segment depression at the onset of angina remained unchanged with placebo and 2.5 or 6.5 mg of SRNG. These results were in agreement with earlier studies on SRNG or isosorbide dinitrate.[3,10]

Previous studies have shown a variable effect of nitrates on rate-pressure product.[11,13,14] Heart rate and systolic blood pressure are important determinants of myocardial oxygen requirement, but these 2 variables do not take into account the influence of ventricular volume and myocardial contractility. In our study, the effects of SRNG on these 2 parameters were not studied. Therefore, we cannot comment on the overall effects of different doses of SRNG on the myocardial oxygen supply and demand equation in the patients studied. It is nevertheless admitted that nitroglycerin improves maximal exercise tolerance mainly by a decrease in venous and arterial tone.

In conclusion, our results show that a single dose of 6.5 mg of SRNG is effective during at least 5 hours, as opposed to a single dose of 2.5 mg. Both the magnitude and the duration of the beneficial effect are dose-related.

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Prolonged Angina Pectoris and Persistent Negative T Waves In the Precordial Leads: Response to Atrial Pacing and to Methoxamine-Induced Hypertension

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In 18 consecutive patients without a history of myocardial infarction (MI), prolonged angina pectoris with persistent negative T waves in the precordial leads was associated with a high frequency of in-hospital spontaneous angina (14 of 18, 78%), usually accompanied by S-T segment elevation, and occasionally in-hospital MI (4 of 18, 22%). Angina and MI always involved the electrocardiographic leads with negative T waves. Coronary arteriography, performed in 16 patients, revealed ≥90% proximal diameter reduction of the left anterior descending (LAD) coronary artery in 14 patients. No patient had severe narrowing of all 3 major coronary arteries, but the 3 who had 100% LAD occlusion lacked collateral circulation. The ejection fraction was ≥50% in 13 patients. Atrial pacing performed in 11 patients at an average rate of 142 beats/min produced a 1.0 mm S-T segment change in only 5 patients (45%), 3 of whom had an associated lactate production. Arterial systemic hypertension induced by methoxamine in 14 patients caused reversal of negative T waves without significant S-T segment shifts or chest pain and failed to elicit lactate extraction abnormalities in each of the 5 patients in whom it was determined. Thus, prolonged angina with persistent negative T waves in the precordial leads is almost invariably associated with a critical and proximal LAD obstruction, severe narrowing of 1 or 2 coronary arteries, and poor or absent collateral vessels. The relatively preserved coronary reserve in 55% of our patients suggests that negative T waves do not represent active myocardial ischemia. The study also suggests that transient "positivization" of the negative T waves may not necessarily relate to myocardial ischemia when associated with acute systemic hypertension.

Although it is known that prolonged angina may be associated with negative T waves in the precordial leads as the only electrocardiographic abnormality,[1–5] the clinical and coronary arteriographic characteristics of these patients are ill defined. Given their electrocardiographic similarities, it is forseeable that these patients also could share common angiographic features which therefore could be predicted from the electrocardiographic findings. Albeit no definite proof has been afforded, perhaps the most accepted hypothesis suggests that these negative T waves reflect subendocardial or transmural ischemia provided the enzyme profile is unaltered.[1,6,7] If this concept were to hold true, it would probably follow that modest increases in myocardial oxygen needs could easily magnify the extent of this ischemia.

Partial or complete T-wave "positivization" however, has been associated with angina and scintigraphic evidence of transmural ischemia,[7–9] but similar electrocardiographic changes during exercise stress testing have been interpreted as nonspecific.[10,11] We surmise that factors other than myocardial ischemia (MI), such as arterial hypertension or the sympathoadrenergic discharge during both spontaneous angina and exercise[12,13] may exert some influence on these changes in T-wave polarity irrespective of the presence of ischemia. The 3-fold purpose of this study is (1) to study the clinical and angiographic characteristics of patients with prolonged angina and negative T waves in the precordial leads, (2) to explore the possibility that these negative T waves could imply a marked reduction in the coronary reserve, and (3) to investigate the effects of arterial systemic hypertension on negative T waves and its correlation with possible symptoms or changes in myocardial metabolites.

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TABLE I Clinical Data

Pt	Age (yr) & Sex	AP	SH	DM	Peak CPK (IU/liter)	Tc (0–4+)	Duration AP (min)	In-H AP Episodes (n)	In-H AMI	Follow-Up Months	AP	MI	CABG	Survival
1	60M	21 d	+	0	43	0	90	8	0	45	0	0	+	+
2	54M	1 y	+	0	149	. . .	20	5	0	42	0	0	0	+
3	46M	60 d	0	0	48	1+	15	6	+	39	+	0	+	+
4	46F	1 y	+	+	43	. . .	20	3	0	38	0	0	0	+
5	49M	60 d	+	0	52	. . .	40	2	0	38	+	0	0	+
6	64M	60 d	0	0	40	. . .	60	1	0	35	+	+	+	+
7	72M	30 d	+	0	23	. . .	40	9	0	33	+	0	0	+
8	68F	11 d	+	0	45	0	20	1	+	20	+	0	0	+
9	60F	60 d	+	+	22	. . .	20	. . .	0	21	+	0	0	+
10	42M	0	0	0	24	0	45	. . .	0	21	0	0	0	+
11	55M	0	0	0	126	. . .	90	1	0	18	+	?	+	0
12	58M	7 y	+	0	32	. . .	120	. . .	0	16	0	0	0	+
13	43F	45 d	0	0	37	. . .	20	5	0	12	0	0	0	+
14	40M	15 d	0	0	142	1+	20	. . .	0	19	+	0	0	+
15	61M	300 d	0	0	27	0	25	13	+	10	0	0	0	+
16	46M	15 d	0	0	102	1+	150	1	+	6	+	0	+	+
17	53M	0	0	0	64	. . .	150	17	0	5	+	0	0	+
18	54M	15 d	0	0	47	. . .	45	1	0	3	+	0	0	+

AMI = acute myocardial infarction; AP = angina pectoris; CABG = coronary artery bypass grafting; d = days; DM = diabetes mellitus; In-H = in-hospital; MI = myocardial infarction; Pt = patient; SH = systemic hypertension; Tc = technetium pyrophosphate scintigram; y = years.

Methods

Patients: The 18 consecutive patients included in this study, 14 men and 4 women, mean age 53 years (range 40 to 72), were admitted within 12 hours of the onset of an episode of prolonged angina (>20 minutes) which was not relieved by sublingual nitroglycerin, 1.0 mg. In addition, they met the following criteria: (1) presence of negative T waves ≥3.0 mm in 2 or more precordial leads involving at least leads V_2 and V_3 or V_3 and V_4, which persisted for a minimum of 3 days; (2) absence of previous MI; (3) absence of acute MI based on the absence of Q waves and the lack of a significant increase in enzyme levels (greater than twice the normal values, 30 to 70 IU/liter); (4) absence of bundle branch block or atrioventricular block of second degree or greater; and (5) absence of valvular heart disease. Patients with variant angina with typical circadian rhythm, a high incidence of nocturnal attacks, and preserved exercise capacity were excluded. Also excluded were those treated with digitalis, amiodarone, or propranolol, those with hypocalcemia, and those with persistent atrial fibrillation.

Protocol: All patients were admitted to the coronary care unit and placed on bed rest. A standard 12-lead electrocardiogram was taken on admission, at least once each day thereafter, and during and after episodes of chest pain. No antianginal medication was administered except for sublingual nitroglycerin or intravenous analgesics. After documentation of the electrocardiographic and blood pressure changes during 1 or 2 episodes of angina, treatment was initiated with nifedipine, 40 to 80 mg/day, isosorbide dinitrate, 5 mg every 2 to 4 hours, or a combination of both drugs. Eventually, some patients also received diltiazem in doses up to 240 mg/day. Total creatinine phosphokinase and oxaloacetic transaminase were measured every 8 hours during the first 48 hours and in the 24 hours subsequent to an episode of angina >30 minutes.

A technetium-stannous pyrophosphate myocardial scintigram (Dynacamera 2C, Picker) was performed between the first and fifth days in 7 patients, using 20 mCi of technetium-99 pyrophosphate. Scans were taken the first and second hours after injection, and images were obtained in 3 different views: anteroposterior, left lateral, and left anterior 45° oblique. They were interpreted by 2 observers unaware of the patient's condition, as follows: 0 = absence of myocardial activity; 1+ = minimal cardiac activity; 2+ = definite myocardial activity but of lesser intensity than that of bone; 3+ = myocardial activity equal to that of bone; and 4+ = myocardial activity greater than that of bone.

Between the 5th and 10th days, and while the electrocardiogram still exhibited negative T waves, 11 patients underwent atrial pacing and methoxamine-induced arterial hypertension studies. Antianginal medication was discontinued at least 6 hours before these tests. After sedation with 5 to 10 mg of diazepam orally, right-heart catheterization was performed using a 7Fr Swan-Ganz catheter inserted percutaneously through the subclavian or femoral vein. An 18-gauge arterial cannula was inserted into a radial or femoral artery for pressure measurements and blood sampling. Pressure was measured through a pressure transducer (Hewlett-Packard, model 1280C). Values were taken at the end-expiratory point averaging 3 respiratory cycles and were recorded on a Hewlett-Packard 4-channel recorder, model 7754. The zero point was measured at the mid-chest level. Cardiac output was measured in triplicate by the thermodilution technique (Edwards Laboratory computer model 9510). In addition, a 7Fr Gorlin coronary sinus pacing catheter (USCI) was introduced into the left subclavian vein, also percutaneously, and advanced into the coronary sinus, placing the tip at the very

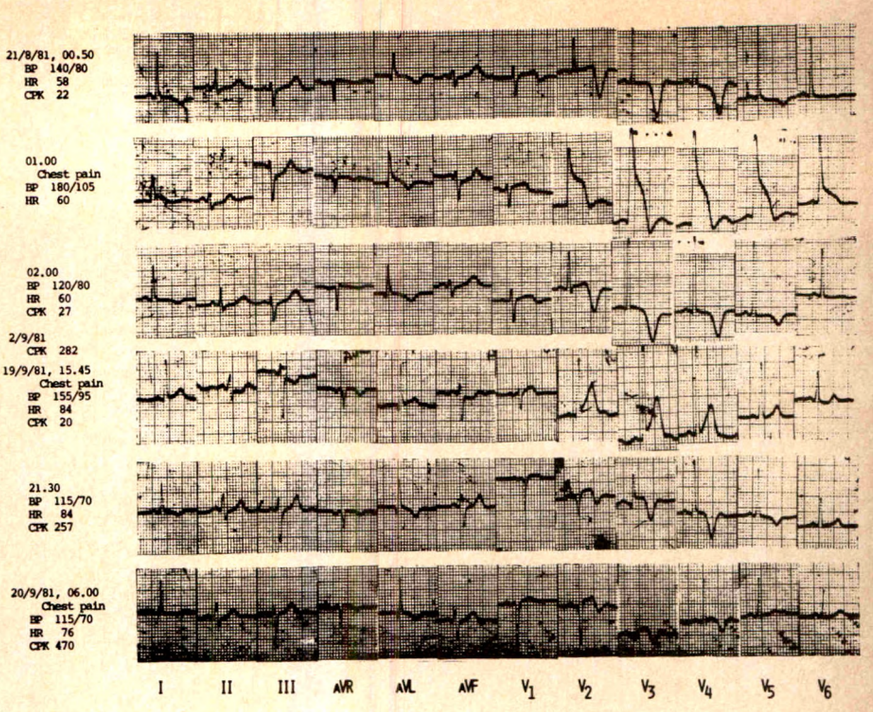

FIGURE 1. Sequential electrocardiograms in Case 15 illustrating changes during several episodes of spontaneous chest pain. Two were prolonged and were followed by QRS changes of transmural myocardial infarction and by an elevation in enzyme levels. The first of these 2 episodes (not shown) occurred on September 1, 1981 and had a peak creatinine phosphokinase of 282 IU/liter and the second, on September 19, had a peak creatinine phosphokinase of 470 IU/liter. BP = blood pressure; CPK = creatine phosphokinase; HR = heart rate.

origin of the coronary sinus to permit pacing as well as blood sampling. In the 7 patients in whom the pulmonary catheter was introduced through the subclavian vein, this catheter was removed before insertion of the Gorlin catheter.

The pacing study was then initiated by increasing the heart rate in steps of 10 beats, which were maintained for 2-minute periods, and stopping during the 10 to 15 beats after each step before going to the next to recognize possible ischemic changes. Pacing was discontinued whenever a 1.0 mm S-T segment shift was observed, a heart rate of 150 to 160 beats/min had been reached, or the patient experienced angina. Allowing a minimum of 20 minutes for recovery and once the possible electrocardiographic changes had fully reverted, an intravenous infusion of methoxamine was started at a rate of 2.0 mg/min with the purpose of increasing systolic blood pressure to a level 30% higher than the baseline value and to maintain it for a 5-minute period. Methoxamine was then discontinued, and 5 minutes later sublingual nitroglycerin, 1.0 mg, was given to accelerate the return of blood pressure to controls levels. Heart rate was kept at approximately the baseline value either spontaneously or by atrial pacing. In 10 patients (Patients 8 to 13, and 15 to 18), simultaneous blood samples were drawn from the arterial line and the coronary sinus catheter to analyze partial pressure of oxygen and carbon dioxide, pH, and plasma potassium at the following time intervals: (1) before pacing (first control), (2) just before stop-

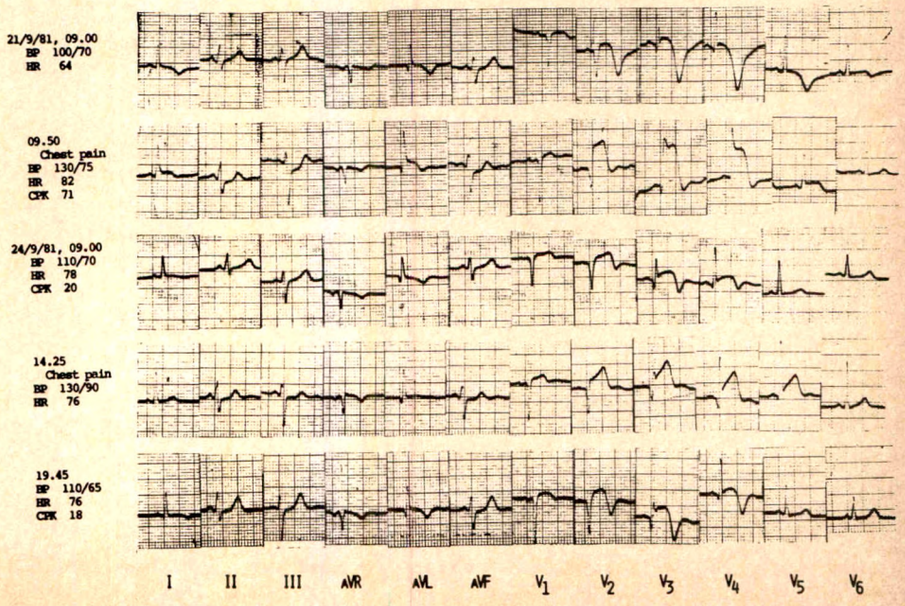

FIGURE 2. Sequential electrocardiograms also in Case 15 illustrating 2 anginal episodes that occurred after the infarction shown in Figure 1. As in previous ischemic episodes, the salient change was S-T segment elevation in the leads with resting negative T waves. Abbreviations as in Figure 1.

ping pacing at the highest rate, (3) before initiating the methoxamine drip (second control), (4) just before stopping methoxamine, and (5) 10 minutes later, after blood pressure had regained baseline values (third control). In 5 patients (Patients 8 to 10, 12, and 18), additional samples for lactate measurements were drawn at the same time intervals. In 6 other patients, only right-heart catheterization and the methoxamine test were carried out.

Blood gases were measured in an ABL-I acid-base laboratory automatic analyzer (Radiometer Copenhagen). Blood lactate was measured using an enzymatic technique.[14] Throughout the pacing and methoxamine studies, the electrocardiogram was continuously monitored on an 6-channel Elema-Mingograf ink jet recorder.

Coronary arteriography and left ventriculography were performed within 15 days of admission in 13 patients and within 30 days in 3 others. Statistical analysis was performed using Student's t test for paired samples.

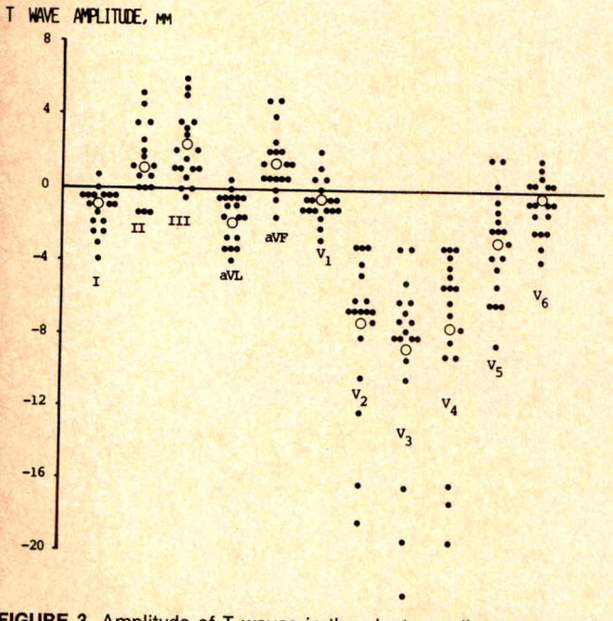

FIGURE 3. Amplitude of T waves in the electrocardiogram of each patient which evidenced the deepest T waves. **Open circles** represent mean values in each lead in the 18 patients, whereas **closed circles** represent individual values.

Results

Clinical features: Relevant clinical data are summarized in Table I. Most patients related a short history of effort or resting angina, or both. Four patients had a history of definite and 4 borderline systemic hypertension. While in the hospital, 14 patients had at least 1 episode of spontaneous angina associated with transient electrocardiographic changes. Myocardial scintigrams were not indicative of MI in the 7 patients in whom they were performed (0 or 1+). In 4 patients, transmural MI developed in the hospital, anterior and uncomplicated in all, and in none did the total creatinine phosphokinase reach 700 IU/liter. In patient 3, MI occurred shortly after coronary bypass grafting. Patients 15 and 16 had a second MI 18 and 7 days after the initial one, involving the same electrocardiographic leads (Fig. 1 and 2).

Electrocardiographic findings: The maximal amplitude of negative T waves, measured at least 12 hours after an eventual episode of rest angina, is shown for each patient in Figure 3. In all patients, leads V_2 to

TABLE II Coronary Arteriographic, Left Ventriculographic, and Electrocardiographic Findings

	Coronary Arteriography: Diameter Reduction (%)				Left Ventriculography		ECG—Negative T Waves		
Pt	LM	LAD	LC	R	Wall Motion	EF (%)	Leads Involved	Maximal Change (mm)	Duration (days)
1	<50	95	<50	<50	Normal	64	I, aVL, V_2–V_6	9.0, V_3	19
2	<50	95	<50	75	Normal	65	I, aVL, V_2–V_4	16.0, V_2	17
3	<50	95	<50	50	Normal	65	aVL, V_2–V_4	8.0, V_3	4
4	<50	100	<50	<50	Ap AK AI HK	45	I, aVL, V_2–V_5	8.0, V_4	10
5	<50	60	75	<50	Ap DK AI HK Dp HK	50	aVL, V_1–V_5	16.0, V_3	18
6	<50	95	<50	80	Normal	68	aVL, V_1–V_5	26.0, V_3	60
7		...			...	...	aVL, V_1–V_4	3.5, V_3	20
8		...			...	...	I, aVL, V_2–V_5	5.0, V_3	15
9	<50	90	<50	<50	Ap HK	62	V_1–V_5	7.0, V_3	5
10	<50	<50	<50	<50	Ap HK	60	V_2–V_4	6.0, V_3	10
11	<50	90	90	<50	Ap HK	55	I, II,aVF, V_2–V_6	6.5, V_3	22
12	<50	100	75	<50	Ap HK	55	I, aVL, V_1–V_5	8.0, V_3	5
13	<50	90	<50	100	Ap DK AI HK Dp HK	45	I, II, aVL, V_2–V_5	8.0, V_3	24
14	<50	95	<50	<50	Ap HK	60	V_2–V_4	3.0, V_3	7
15	<50	95	<50	<50	Ap HK	64	I, aVL, V_2–V_5	19.0, V_3	20
16	<50	95	70	<50	Ap HK	65	I, II, aVL, V_2–V_6	9.0, V_4	15
17	<50	100	<50	<50	Ap AK AI AK Dp HK	40	aVL, V_2–V_4	10.0, V_3	3
18	<50	90	<50	<50	Normal	70	V_1–V_5	7.0, V_3	3

AK = akinesia; AI = anterolateral; Ap = apical; DIST = distal; DK = dyskinesia; DP = diaphragmatic; EF = ejection fraction; HK = hypokinesia; LAD = left anterior descending artery; LC = left circumflex coronary artery; LM = left main coronary artery; Pt = patient; R = right coronary artery.

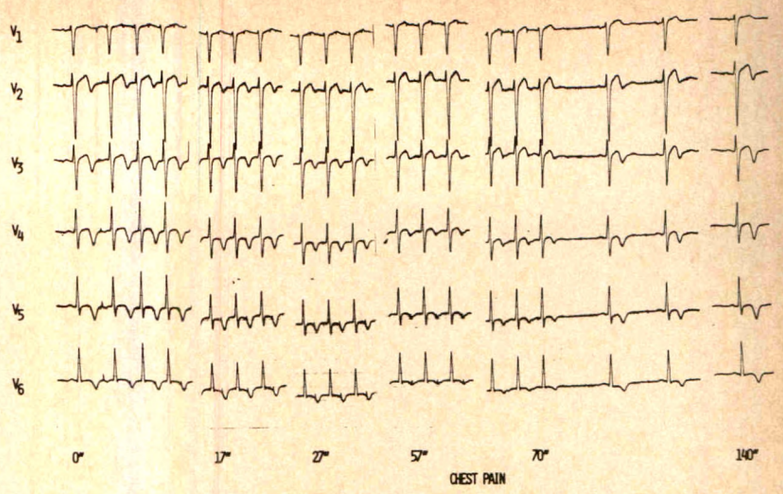

FIGURE 4. Effects of atrial pacing at a rate of 150 beats/min on negative T waves in Case 16. The progressive disappearance of negative T waves is probably indicative of ischemia which culminates in chest pain and a 2.0-mm S-T segment elevation in V_2 which already had a 1.0-mm elevation in the resting electrocardiogram. The changes reverted in <2 minutes and pain was immediately relieved on cessation of pacing. Disappearance of negative T waves is partly related to the superimposition of the P wave on the T wave during pacing.

V_4 had negative T waves. In 12 of them, negative T waves persisted >9 days, and in 5 they persisted ≥20 days. In each of the 14 patients who had ≥1 episodes of spontaneous angina, S-T segment elevation was present in leads with negative T waves in at least 1 crisis. In other anginal episodes, only complete or partial positivization of T waves was observed. Myocardial infarction and reinfarction involved leads with negative T waves. Only 3 patients had an electrocardiographic pattern of left ventricular hypertrophy in the resting electrocardiogram. All patients remained in sinus rhythm.

Coronary arteriographic findings: Fourteen of the 16 patients who underwent coronary angiography presented ≥90% diameter reduction of the proximal segment of the left anterior descending (LAD) coronary artery (Table II). Three had 100% occlusion, and 1 remaining patient had 50 to 60% proximal LAD stenosis and the other had 75% obstruction of the first diagonal branch as the only significant lesion. No patient had significant (≥70%) 3-vessel disease (LAD, left circumflex coronary artery, and right coronary artery). Collateral circulation was nonexistent in 13 patients and present in 3 who happened to have 100% LAD occlusion. However, in 2 of them this collateral supply was poor. In Patients 6 and 14, a second coronary arteriography was carried out 2 years later, revealing complete occlusion of the initially critical LAD stenosis, progression of the disease in other vessels, and the appearence of collateral vessels. Twelve patients had either a normal left ventriculogram or slight apical hypokinesia. Ejection fraction was ≥50% in 13 patients. One of the 2 patients without coronary angiograms (Patient 8) had an in-hospital MI and early postinfarction angina.

Pacing test: During right-sided cardiac catheterization, 6 patients had angina which reverted spontaneously or after sublingual nitroglycerin. In these patients, pacing and pressure measurements were not taken earlier than 30 minutes after relief of angina. Baseline right atrial and left ventricular filling pressures were normal (4.6 ± 0 and 8.9 ± 1 mm Hg, respectively; mean ± standard error of the mean). Cardiac index was

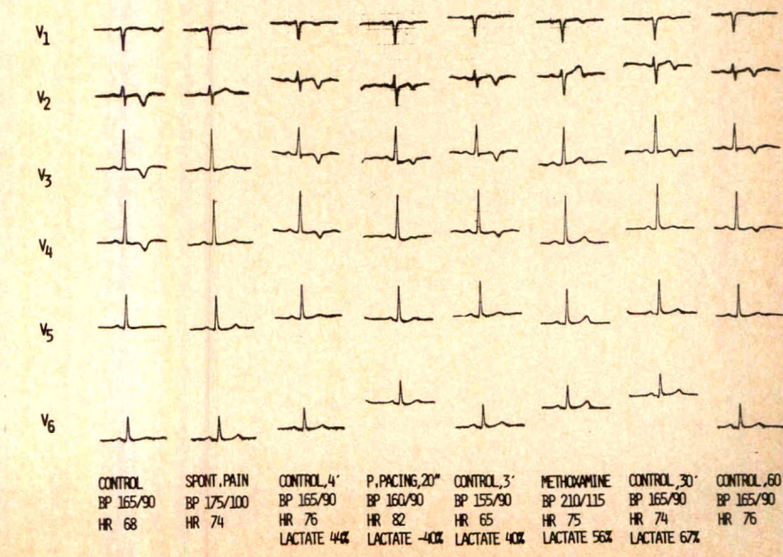

FIGURE 5. Changes in precordial leads, blood pressure (BP), and heart rate (HR) during spontaneous angina (Spont. pain) 20 seconds after pacing at 150 beats/min (P. Pacing, 20"), during methoxamine-induced hypertension, and during appropriate control measurements in Case 18. Results of lactate extraction measured at several of these steps are also shown. Right after pacing there is a reduction of negative T waves, a 1.0-mm S-T segment depression in leads V_3 and V_4, and an important lactate production, whereas during methoxamine there is an absence of significant S-T segment changes and of lactate production despite an indisputable T-wave positivization similar to that occurring during spontaneous angina. In this case, however, elevation of the J point does not permit some degree of ischemia to be ruled out. The electrocardiographic changes rapidly disappear after pacing ceases and after prompt relief of pain with nitroglycerin in spontaneous angina, whereas those related to methoxamine persisted through the first 30 minutes. An additional sample for lactate metabolism was drawn as soon as the electrocardiogram had returned to control after pacing (Control 3').

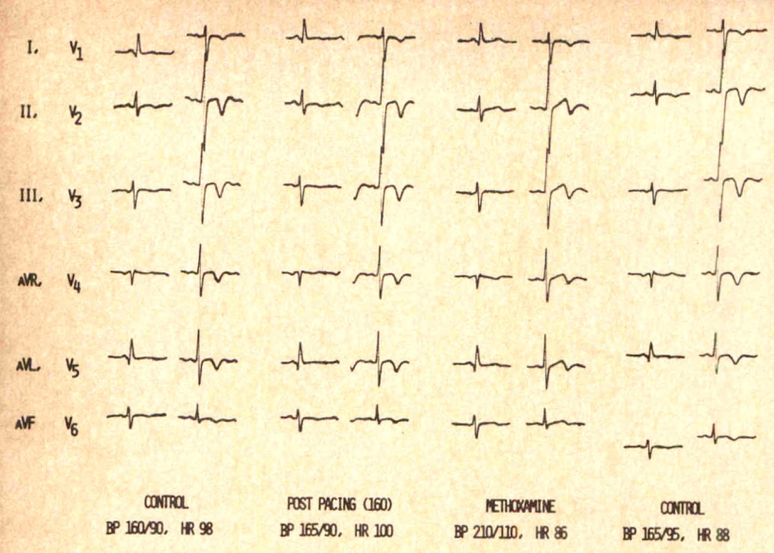

FIGURE 6. Changes in the 12-lead electrocardiogram in Case 13 a few seconds after maximum heart rate by pacing and during methoxamine infusion. This patient developed neither T-wave nor S-T segment changes during pacing. During hypertension, there were also no significant (≥1.0 mm) S-T segment changes or chest pain; T-wave changes, nevertheless, became apparent. Appreviations as in Figure 1.

also normal in most of the 12 patients in whom it was measured. During pacing, 1.0 mm S-T segment depression developed in 5 patients. One also developed a 1.0 mm S-T segment elevation. In Patient 12, pacing could not proceed beyond 100 beats/min because of Wenckebach atrioventricular block. Four patients had chest pain which disappeared after cessation of pacing. During pacing the magnitude of negative T waves tended to decrease particularly among those who developed S-T segment changes. (Fig. 4). The duration of all electrocardiographic changes did not exceed 15 minutes. Three patients (Patients 8, 9, and 18) of the 5 in whom lactate metabolism was studied, exhibited lactate production associated with significant S-T segment shifts (Fig. 5).

Methoxamine test: Administration of this drug produced substantial systemic hypertension: systolic blood pressure increased from 140 ± 5 to 208 ± 6 mm Hg and diastolic blood pressure from 74 ± 2 to 110 ± 3 mm Hg, and was not accompanied by chest pain or significant (≥1.0 mm) S-T segment changes. However, in 3 patients, it elicited an almost significant J point elevation in lead V_2. Total dose of methoxamine ranged from 15 to 30 mg. Three of 17 patients in whom the test was performed were excluded from the electrocardiographic analysis due to unacceptable recordings. In each of the remaining 14 patients the amplitude of negative T waves was reduced, and in several a definite T-wave positivization followed (Fig. 6). These changes persisted an average of 30 minutes (range 20 to 90) and were associated with an increase in T wave amplitude in other leads with initially flat or positive T waves. These changes differ from those observed during pacing, which

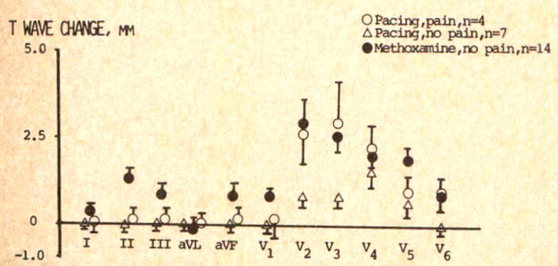

FIGURE 7. Mean (± standard error of the mean) changes in T-wave amplitude during pacing in patients who developed pain (**open circles**), in those who did not develop pain (**open triangles**), and during methoxamine-induced hypertension (**closed circles**) which did not cause pain. Because control precordial leads presented negative T waves, the increased amplitude actually represents a decrease in negativity, whereas in leads II, III, and aVF with control positive T waves, the change means a net increase in their amplitude. The tendency to become less negative or more positive during methoxamine is clear in most leads although it is more evident in leads V_2 through V_5. In contrast, during pacing, T-wave changes were limited to precordial leads and were of little magnitude, particularly in patients who did not present chest pain.

TABLE III Methoxamine and Pacing Studies: Metabolic Data (Mean ± SEM)

		Blood Gases (n = 10)			Lactate Extraction (%) (n = 5)
		PO_2 (mm Hg)	PCO_2 (mm Hg)	pH (Units)	
Control	A	72 ± 2	39 ± 1	7.38 ± 0.01	32 ± 14
	Cs	21 ± 1	51 ± 1	7.34 ± 0.01	
Pacing	A	79 ± 4	38 ± 2	7.40 ± 0.01	11 ± 23
	Cs	20 ± 1	51 ± 1	7.35 ± 0.01	
Control	A	70 ± 3	38 ± 1	7.39 ± 0.01	37 ± 12
	Cs	19 ± 1	49 ± 1	7.36 ± 0.01	
Methoxamine	A	75 ± 2	38 ± 1	7.41 ± 0.01	52 ± 5
	Cs	19 ± 1	52 ± 1	7.35 ± 0.01	
Control	A	71 ± 3	38 ± 1	7.41 ± 0.01	39 ± 9
	Cs	19 ± 4	49 ± 2	7.37 ± 0.01	

A = arterial; Cs = coronary sinus; PCO_2 = arterial carbon dioxide tension; PO_2 = arterial oxygen tension; SEM = standard error of the mean.

were confined to leads with negative T waves (Fig. 7). Positivization of T waves during methoxamine administration was not modified by the administration of sublingual nitroglycerin. Left ventricular filling pressure (pulmonary artery diastolic pressure) increased during hypertension in each of 9 patients in whom it was monitored (7.9 ± 1 to 17.4 ± 1 mm Hg) and returned to control levels on normalization of blood pressure. In Patient 17, pacing and methoxamine studies were performed once T waves had become upright. This patient had a slight increase in T wave amplitude and a 1.0 mm S-T segment shift localized in leads within negative T waves during pacing-induced angina, and generalized and persistent increases in T wave amplitude without pain or S-T segment changes during methoxamine perfusion.

In none of the 5 patients in whom lactate metabolism was studied were there abnormalities in lactate extraction during hypertension (Table III). In addition, no increases in plasma creatinine phosphokinase levels occurred during the ensuing 24 hours in the 5 patients in whom they were determined to rule out possible myocardial damage caused by methoxamine. In the 10 patients in whom coronary arteriovenous differences in the partial pressure of oxygen and carbon dioxide, pH, and potassium were examined, no significant differences were observed during pacing and methoxamine tests (Table III) with regard to control measurements. However, arterial partial pressure of oxygen and oxygen extraction tended to increase during both interventions, and coronary sinus partial pressure of carbon dioxide also tended to increase during hypertension. No complications occurred during either test.

Follow-up: During an average follow-up of 23 months (range 3 to 45) 1 patient had inferior MI and another died during coronary surgery (Table I). Ten patients had effort angina and 8 also had resting angina despite treatment with nitrates and calcium antagonists.

Discussion

Patients with coronary artery disease who have prolonged chest pain associated with persistent negative T waves in the precordial leads and normal enzymes have been included in the series of unstable angina without attempting to single out their possible clinical and angiographic characteristics.[15,16] Clinically, most of our patients had a short history of effort or rest angina, or both, and had episodes of spontaneous angina while in the hospital. Four patients developed acute, anterior, transmural, and uncomplicated MI during hospitalization. During an average follow-up of 23 months, 1 patient died, another had inferior MI, and 10 continued to have angina. With an overall 2-year mortality rate of 5% and a MI rate of 28%, these patients seemed to have a rather good long-term prognosis despite an initial unstable course. Gazes et al[3] pointed out the relative low risk in their 32 patients after a 10-year follow-up. Their MI and mortality rates were somewhat lower than ours, but they included patients with negative T waves in precordial as well as nonprecordial leads and patients who had negative T waves during resting angina. Earlier, Pruitt et al[1] commented that their 62 patients with negative T waves in the precordial leads presented recurring episodes of spontaneous angina, as did ours. Cutts et al,[2] in 69 patients comparable to ours, noted that prognosis was poor, reporting a 4-year mortality rate of 20%, half of their deaths occurring during the first year. None of the foregoing studies had arteriographic data.

Three of the 5 patients reported on herein who had an in-hospital MI had recurring episodes of resting angina before the acute MI. Therefore, their course was similar to that described by Madias[7] and Maseri et al[17] in a group of patients in whom MI eventually developed after several crises of spontaneous angina during hospitalization. Most of their patients also had negative T waves in the precordial leads before MI. These investigators attributed both resting angina and MI to coronary spasm,[7,17] a factor not ruled out in our patients.

Our angiographic observations constitute the first prospective report on this subject. These findings, which in essence indicated ≥90% proximal stenosis of the LAD, severe 1- or 2-vessel narrowing, absence of collaterals, and preserved left ventricular function, agree with those of Fisch et al,[5] who were the first to draw attention to isolated and severe LAD disease and to the lack of collaterals in 6 similar patients. Arteriographic data extracted from other series of patients with unstable angina, which included patients with negative T waves in the precordial leads, also bear out our observations.[18–20] Likewise, Batlle et al[4] reported the association of prolonged angina, negative T waves, proximal single- or double-vessel disease, and poor collateral vessels, although they failed to mention the localization of negative T waves and of the coronary lesions.

Although important and proximal LAD stenoses are also present in most patients who develop S-T segment elevation in the precordial leads during angina,[7,17,21] the degree of this LAD narrowing is not consistently as critical as it is in patients with negative T waves. This fact is infered from studies of patients with unstable angina who had resting electrocardiographic abnormalities other than negative T waves.[5,7,9] This close relation between negative T waves and severe LAD stenosis is further substantiated by the work of McMahon et al[21] who found negative T waves in the precordial leads in each patient in a restricted group selected on the basis of 95% proximal LAD obstruction, single-vessel disease, no collaterals, and the absence of previous MI.

Isolated negative T waves associated with elevated cardiac enzymes[22,23] or pathologic evidence of tissue necrosis[1,24] has been interpreted as a sign of subendocardial necrosis. However, in our patients it is somewhat difficult to consider such a diagnosis for they had no enzyme elevation and no positive scintigraphic findings, although scintigraphic data were only available in some cases.[25] When associated with prolonged angina and no evidence of MI, negative T waves are believed to indicate subendocardial or transmural ischemia.[1,6,7] If this were the case, slight or moderate increases in myocardial oxygen needs in these circumstances would readily in-

crease the severity of ischemia. Contrary to this hypothesis, however, we found that a considerable proportion of our patients were able to withstand pacing rates that commonly cause ischemia in other patients with unstable or even stable engina,[26,27] without exhibiting S-T segment changes or chest pain. This relatively high threshold for ischemia may question the validity of the ischemic nature of these negative T waves in at least some patients. In similar cases, absence of ischemic changes were found in biopsy studies of the myocardial tissue underlying the electrocardiographic leads with negative T waves.[28]

In 4 of the 5 patients in whom an electrocardiogram was recorded during prolonged angina, S-T segment elevation also was documented in the leads with subsequent negative T waves. In addition, S-T segment elevation also was observed during spontaneous angina in the leads with negative T waves in 12 patients. Madias[7] and Maseri et al[18] reported similar findings during pain in comparable patients. Therefore, negative T waves in the setting herein discussed may imply recent but not actual transmural ischemia.[1] Therefore, we submit that most episodes of prolonged angina are transient transmural ischemia.

In accordance with previous investigators,[7–9] we documented upright T waves as the sole electrocardiographic changes during some episodes of spontaneous angina which has also been shown to indicate transmural myocardial ischemia in scintigraphic studies.[19] However, interpretation of identical partial or complete positivization of negative T waves during symptomless exercise-stress test remains controversial.[10,11,29,30] Contrary to earlier opinions,[29,30] observers are currently inclined to confer no pathologic significance on to such transient electrocardiographic changes.[10,11] Because of this discrepancy, we examined the possibility whether this electrocardiographic change could be accounted for at least in part by the increases in blood pressure so often present during exercise and angina.[12,13] We found that hypertension did indeed produce a decrease in T-wave negativity and frequently a complete positivization. We doubt that this reversal of negative T waves by methoxamine in most patients signifies myocardial ischemia relative to the increase in myocardial oxygen demands due to hypertension, because it was not generally associated with significant S-T segment changes, chest pain, or lactate production whenever measured, and moreover was not modified by nitroglycerin. Previous studies have demonstrated that drug-induced hypertension cannot elicit myocardial ischemia in patients with angina and fixed coronary narrowings.[31,32] Whether the persistence of negative T waves implies a state of adrenergic imbalance with abnormal sympathetic activity that could in turn be responsible for recurrence of paroxysmal increases in coronary arterial tone and subsequent ischemia[33] is an attractive hypothesis that cannot be validated from our data. However, along with this theory is recent evidence of the existence of alpha-adrenergic receptors in the myocardium,[34] and recent work has attributed to methoxamine an alpha constrictor activity[35] and a capacity to increase contractility which can be completely prevented by alpha-adrenergic blockage.[34] These developments may allow speculation on the possible neurogenic nature of the negative T waves and on the likelihood that its reversal by methoxamine could have been due to a direct alpha-adrenergic effect perhaps also present during exercise or rest angina.

The rather preserved coronary reserve as suggested by the nonischemic response to pacing and hypertension in an appreciable number of patients may reflect certain improvement in the resting cardiac reserve afforded by the use of calcium antagonists or nitrates despite the fact that treatment was withheld 6 hours before these studies.

Increases in arterial partial pressure of oxygen and oxygen extraction were observed during pacing and during hypertension. These changes might possibly be ascribed to reflex hyperventilation secondary to mild lung congestion because of hampered left atrial emptying during pacing and to increases in left ventricular filling pressure during hypertension. More obscure is the interpretation of increases in coronary sinus partial pressure of carbon dioxide during methoxamine. A drug-linked reduction in coronary flow offers a possible explanation which could also account, at least in part, for the increases in oxygen extraction.

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Clinical Evaluation of the Internal Automatic Cardioverter-Defibrillator in Survivors of Sudden Cardiac Death

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An R-wave synchronous implantable automatic cardioverter-defibrillator (IACD) was evaluated in 12 patients with repeated episodes of cardiac arrest who remained refractory to medical and surgical therapy. Seven men and 5 women, average age 61 years, surgically received a complete IACD system. Coronary artery disease was found in 11 and the prolonged Q-T syndrome in 1. The average ejection fraction was 34%, and 6 patients had severe congestive heart failure (New York Heart Association class III or IV).

The IACD is a completely implantable unit consisting of 2 bipolar lead systems. One system uses a lead in the superior vena cava and on the left ventricular apex through which the cardioverting pulse is delivered. The second system employs a close bipolar lead implanted in the ventricle for sensing rate. After the onset of ventricular tachycardia or fibrillation, the IACD automatically delivers approximately 25 J.

Postoperative electrophysiologic study in 10 and spontaneous ventricular tachycardia in 1 patient demonstrated appropriate IACD function and successful conversion in all with an average of 18 ± 4 seconds. The induced arrhythmias were ventricular tachycardia (160 to 300 beats/min) in 9 and ventricular fibrillation in 1.

These data demonstrate that ventricular tachycardia, not ventricular fibrillation, was the predominant rhythm induced during programmed ventricular stimulation in these survivors of cardiac arrest and that the IACD effectively responded to a wide range of ventricular tachycardia rates as well as ventricular fibrillation. Use of the IACD offers an effective means of therapy for some patients who otherwise may not have survived.

As originally conceived,[1] the implantable automatic defibrillator employed in animal studies,[2] and later modified for patient implants,[3] was for automatic conversion of ventricular fibrillation (VF). Both sensing and defibrillation was accomplished by electrodes positioned in the superior vena cava (SVC) and on the left ventricular (LV) apex. The determinant for detection of VF was satisfaction of a probability density function[4] which required the input signal to spend increased time away from a zero-potential baseline. VF, characterized by a sinusoidal pattern, spends relatively little time at the zero potential. With sinus rhythm the signal spends a relatively great amount of time at the zero potential (for example, P-R or T-P segments). As a practical consequence, ventricular tachycardia (VT) rates <240 to 250 beats/min were subject to rejection by the probability density function sensing circuitry since there was increased isoelectric time (the T-QRS segment). It became apparent,[5–8] however, that most survivors of cardiac arrest initially had hypotensive VT with rates <240 beats/min. VF was observed only at a later stage, if at all.

Therefore, extensive design modifications were undertaken to broaden the spectrum of ventricular tachyarrhythmias to which the defibrillator would respond. This was accomplished, in part, through the development of a reliable rate detector system using a bipolar ventricular lead which also served for R-wave synchronization. Thus, the modified defibrillator used the SVC-LV apex for probability density function detection and delivery of the cardioverting pulse, and the

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TABLE I Clinical Characteristics

Patient	Age (yr) & Sex	Ejection Fraction (%)	Previous Antiarrhythmic Therapy	Episodes of Cardiac Arrest (n)	Current Antiarrhythmic Therapy	Other Surgery*
1	72M	37	D, Pa, Prop, Q; Apr	1	Amio	0
2	48F	55	PA, Nife, Dilt	3	PA, Nife, Dilt	0
3	65F	55	D, PA, Prop, Q	10	Apr	0
4	52M	27	DPH, PA, Prop, Q; Nife, Verap; Apr, Flec, Lorc	2	Dilt	An, SER
5	73M	34	PA, Prop, Q, Verap; Apr, Flec	2	Amio	CAB
6	75M	30	D, PA, Prop, Q; Apr	2	Flec	0
7	56M	19	D, Pa, Prop, Q; Amino, Apr	3	0	CAB, An
8	57M	14	DPH, PA, Prop, Q; Dilt, Mex	1	Amio, Apr	0
9	61M	40	D, Q; Mex, Amio, Apr	4	0	0
10	57F	33	D, PA, Prop, Q; Apr	2	0	CAB, An, SER
11	60M	27	DPH, Q, PA, Prop; Apr	2	Apr	0
12	60M	18	D, PA, Q; Apr, Toc	5	PA, Amio	An, SER
13	64F	41	D, PA, Prop, Q;	4	Amio	An, SER
14	49F	49	DPH, Prop, stellate block	3	DPH, Prop	0

An = aneurysmectomy; Amio = amiodarone; Apr = aprindine; CAB = coronary artery bypass graft; D = disopyramide; Dilt = diltiazem; DPH = phenytoin; Flec = flecainide; Lorc = lorcainide; Mex = mexiletine; Nife = nifedipine; PA = procainamide; Prop = propranolol; SER = subendocardial resection; Q = quinidine; Verap = verapamil.

* Performed at time of IACD implant.

ventricular bipolar lead permitted accurate counting of lower heart rates.

This report describes our initial clinical experience with the internal automatic cardioverter-defibrillator (IACD) (Intec Systems, Pittsburgh, Pennsylvania) in patients with refractory, life-threatening ventricular tachyarrhythymias.

Methods

Patient population: Each patient (Table I) considered for IACD implant had previously had failure with several antiarrhythmic agents (average 5.0) and continued to have episodes (average 3) of life-threatening ventricular arrhythmias requiring cardiopulmonary resuscitation. Informed consent was obtained separately for each of the invasive diagnostic procedures and a separate set of consent forms were used both for the surgery to be performed and for implantation of the IACD.

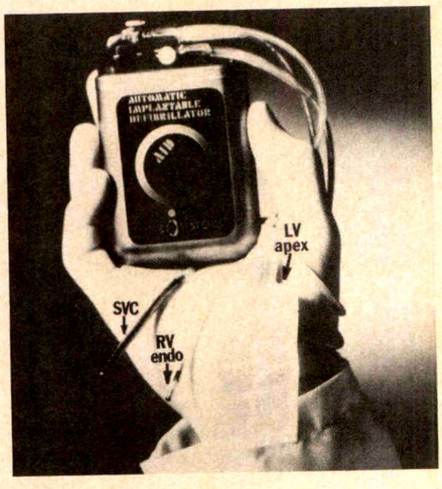

FIGURE 1. IACD pulse generator with the superior vena cava and left ventricular apex electrodes which constitute 1 bipolar system for sensing probability density function and delivery of the cardioverting pulse. The second bipolar lead (RV endo) is used for sensing ventricular rate and R-wave synchronization; this lead may be positioned in the right ventricular apex (as shown), or left ventricular intramural bipolar leads may be substituted.

The clinical features of the patients on whom this report is based are presented in Table I. The average age was 61 ± 8 (standard deviation) years, with 9 men and 5 women. Coronary artery disease was the major cardiac condition in all but 1 patient who had idiopathic prolongation of the Q-T interval (without deafness). The average ejection fraction was 34 ± 13% and significant congestive heart failure (New York Heart Association class III or IV) was present in 9 patients.

Five patients had previously undergone cardiac surgery consisting of aortocoronary artery bypass, aneurysmectomy, and LV subendocardial resection. Two patients (Patients 11 and 12) previously underwent exchange of the older defibrillator model because of battery depletion. A fractured SVC lead was replaced in 1 and a fractured apical lead was replaced in another.

Preoperative evaluation was undertaken in all IACD candidates. This included at least 72 hours of ambulatory electrocardiography, submaximal exercise testing and documentation of antiarrhythmic drug levels. All patients were required to have received conventional antiarrhythmic agents with continued life-threatening ventricular arrhythmias or to have sustained VT induced during programmed electrical stimulation. Propranolol and disopyramide were considered relatively contraindicated if the patient manifested New York Heart Association class III or IV congestive heart failure. Use of investigational antiarrhythmic agents did not preclude implantation of the IACD.

Programmed electrical stimulation was accomplished using a basic ventricular drive (n = 8) of 600, 500, and 450 ms with single and double ventricular premature stimuli of 1.0 ms pulse width at twice diastolic threshold until ventricular refractoriness was reached. Ventricular burst pacing (n = 10) was used at progressively shorter cycle lengths until 2:1 conduction was manifest or until the burst pacing cycle length reached 200 ms. If sustained VT or VF was not induced from the right ventricular apex, the pacing protocol was repeated with the catheter repositioned at the right ventricular outflow tract followed by 2 LV sites.

The internal automatic cardioverter-defibrillator (Fig. 1) is a device with external dimensions of 8.1 × 11.1 × 2.54 cm, weighing 290 g, and having an internal volume of 162 cm^3 with a specific gravity of 1.8. The case is constructed of titanium, is hermetically sealed, and contains a special lithium

battery capable of charging 2 capacitators to approximately 700 V in 7 to 9 seconds.

The IACD employs 2 bipolar electrode systems. One bipolar electrode system serves both for defibrillation and for sensing the probability density function: an intravascular catheter (anode) is positioned in the SVC near the right atrial junction with the cathode having the form of a flexible rectangular patch and placed over the LV apex. The other bipolar electrode system consists of either a right ventricular endocardial catheter (with 1 cm interelectrode spacing) or intramural electrodes which serve for rate detection and R-wave synchronization. Input signal compensation is provided for wide amplitude variations; however, the minimum voltage required for rate sensing is approximately 0.1 mV. When both the probability density function and rate criteria are satisfied, the device delivers a truncated exponential pulse of approximately 6 ms across the SVC and LV patch electrodes. The initial discharge is approximately 25 J, but the IACD can recycle 3 times with the strength of the final 3 pulses increased to 30 J. All discharges are synchronized to the onset of ventricular depolarization detected locally through the rate detector lead, whether this is VT or VF.

When compared with the earlier model,[3] the cardioverter-defibrillator provides several additional features which can be monitored noninvasively after implantation: (1) using a strong external magnet and detector (AIDcheck B®), the number of delivered pulses and capacitator charging time can be measured; (2) if the magnet is held in place above the implanted device, an audible beeping tone is emitted synchronous with the detected R wave, which permits a rapid check of the R-wave sensing function; (3) in addition, the magnet may be used to completely inactivate (or reactivate) the device; and (4) radiodense insignias are incorporated to permit easy identification. As in the previous model, when the IACD is magnetically activated, the pulse is delivered into an internal resistor rather than through the leads to the patient.

Implantation procedure: The surgical approach is dictated by clinical needs and has been previously described.[9] This remains the same except that the bipolar, rate-detector lead is implanted using closely spaced (1 cm) LV intramural electrodes if the patient requires either a median sternotomy or lateral thoracotomy. In those cases approached using a subxiphoid incision,[10] the right ventricular bipolar endocardial rate detector lead is implanted percutaneously in a fashion similar to transvenous pacemaker insertion. The choice of the surgical approach is dictated by the clinical needs. For example, if the patient had not had previous chest surgery and the procedure was only for IACD implantation, the subxiphoid incision was used. On the other hand, if additional surgery (for instance, coronary bypass) was needed or if the patient had previously had chest surgery, then either the lateral thoracotomy or median sternotomy was used. All leads are tunneled subcutaneously and connected to the IACD generator placed in a pocket developed in the periumbical area.

Postoperative evaluation includes general medical management and adjustment of antiarrhythmic therapy. Programmed stimulation was performed postoperatively in all but 2 patients in whom IACD function had been evaluated intraoperatively (Patient 9) or the device responded appropriately to a spontaneous arrhythmia (Patient 14). If programmed stimulation failed to induce a sustained ventricular tachyarrhythmia, it was reliably induced using a 1 to 5 second exposure to full-wave rectified alternating current.[11] These procedures permitted assessment of both the inducibility of the patient by programmed stimulation and the adequacy of IACD function.

Most patients had the implantation procedure performed in 2 stages: the leads were first surgically implanted in the operating room and, after postoperative recovery, the pulse generator was inserted under local anesthesia with testing in the electrophysiology laboratory. This permitted recording of IACD lead signals which were later replayed off-line through a bench model of the IACD. In this manner, the IACD could later be analyzed with respect to both probability density function and ventricular rate-counting accuracy in the individual patient during sinus rhythm and induced tachyarrhythmias.

Patient follow-up procedures required outpatient visits every 8 to 12 weeks for noninvasive testing of the pulse generator in order to reevaluate medical therapy and to assess residual battery life.

Results

Operative results: Three patients had the subxiphoid approach,[10] 4 patients had a left thoracotomy, and 7 patients had a median sternotomy for lead insertion. In 6 patients, aortocoronary artery bypass and aneurysmectomy were performed at the time of IACD lead placement (Table I).

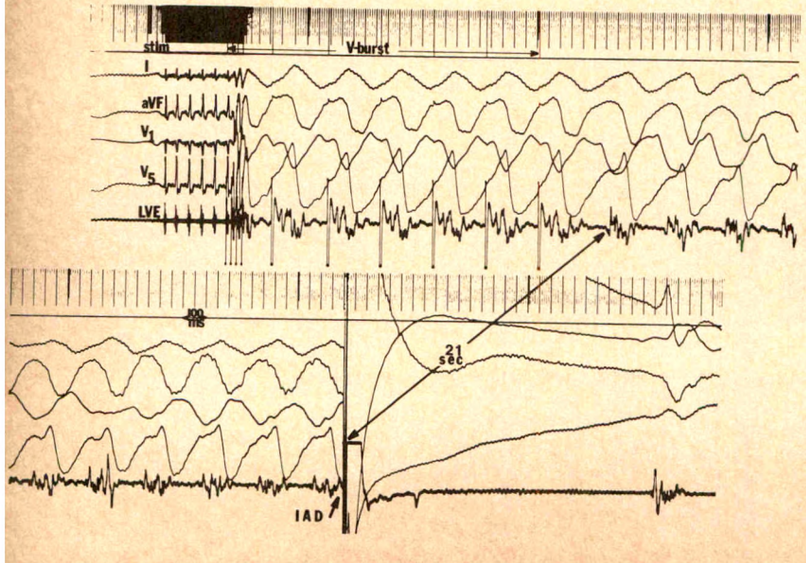

FIGURE 2. Postoperative IACD testing is illustrated with the induction of sustained ventricular tachycardia by programmed stimulation using 10 pulses (V burst; basic cycle length 230 ms). The pacing stimulus (stim) is illustrated with surface leads I, aVF, V_1, and V_5 and a left ventricular electrogram (LVE). From sinus rhythm (slower paper speed), V-burst results in a sustained ventricular tachycardia (240 ms = 250 beats/min) which is automatically terminated with an R-wave synchronous pulse (IAD) 21 seconds later. Within 1.5 seconds after IAD discharge, a perfusing rhythm was restored.

There were no intraoperative deaths. However, 3 patients died in the early postoperative period. Two of these patients (Patients 6 and 7) died in progressive low-output failure before implantation of the IACD pulse generator. The third patient (Patient 9) expired in cardiogenic shock associated with intractable VT during which time the IACD was observed to function appropriately. All 3 patients had severe heart failure preoperatively and postmortem examination revealed no evidence that the implanted leads contributed to these deaths. One patient (Patient 13) had a postoperative thrombosis of the subclavian vein in which the SVC electrode was located. There was complete resolution after heparin therapy.

Electrophysiologic testing: During the pre- and postoperative electrophysiologic studies, there were no complications. Programmed stimulation was performed in all 12 patients who received pulse generators except Patient 9, in whom appropriate spontaneous IACD function was observed. All patients except Patient 14 had VT, and not VF, induced during these studies. Patient 14 was documented to have VF associated with the idopathic prolonged Q-T syndrome, and VF was also induced during programmed stimulation. One patient (Patient 3) had a successful postoperative conversion while taking investigational drugs, and another (Patient 10) had negative programmed stimulation results after coronary artery bypass, aneurysmectomy, and LV subendocardial resection.[12] In those cases (Patients 3 and 10) having negative results by programmed stimulation, alternating current was used for arrhythmia induction to permit IACD testing and resulted in sustained VT. An example from 1 postoperative study is shown in Figure 2.

The IACD system successfully converted malignant ventricular tachyarrhythmias in all 12 patients who had received pulse generators: 1 patient had a spontaneous arrhythmia and 11 were induced. The average IACD charge time (7.5 ± 0.8 seconds) obtained during a magnet test agreed closely with the actual charge time of the IACD (7.3 ± 0.5 seconds) obtained during the electrophysiologic study (Table II). The magnet was initially held in place (which inactivated the IACD) approximately 5 seconds after arrhythmia induction to prevent false sensing during rapid ventricular pacing. Therefore, the total time to defibrillation, which averaged 17.9 ± 4.2 seconds, represents the period of time when the unit was not permitted to detect (that is, magnet in place), plus the requisite amount of time (5 to 7 seconds) for rhythm recognition and the charging time of the capacitators (7.3 ± 0.5 seconds).

Conversion to the patient's normal rhythm was accomplished with a single discharge in 9 of the 12 cases. In 3 cases (Patients 1, 2, and 8) the initial discharge did not convert the rhythm; however, the unit immediately recycled and the second pulse restored the preinduction rhythm. In Patient 8, the initial IACD implanted had a rate setting too high for the induced VT, necessitating replacement with a lower rate cutoff. The latter successfully converted the VT to sinus rhythm in 30 seconds by recycling when the initial discharge was unsuccessful. In none of these cases did the initial discharge cause degeneration to VF and, when the VT

TABLE II IACD Results

Patient	Rate Lead Location	Rate Minimum (beats/min)	Joules*	Electrophysiologic Induced Rhythm (Rate) (beats/min)		Magnet Test Charge Time (s)	Time (s)	Comments
				Preop	Postop		IACD Charge Time/Total Time	
1	RVA	169	24	VT (170)	VT (190)	6.3	6.8/17 (#1)	IACD recycle; BBB
							6.1/15 (#2)	
2	LV	155	23.5	0	VT by AC (250)	7.5	(a) 7.5/15	(a) Failed to charge
							(b) 7.5/24 (#1)	(b) IACD replaced; recycled
							7.0/18 (#2)	BBB; VVI pacemaker
3	LV	159	24	VT (200)	VT by AC (220)	8.2	8.0/15	
4	LV	160	23	VT (140–180)	VT (170)	7.1	7.4/27	...
5	LV	160	23	VT (240)	VT (170)	7.5	7.5/18	...
6	...	...	...	...	...	...	...	Died, postop CHF
7	LV	...	...	...	...	...	...	Died, postop CHF
8	LV	(a) 165	24	VT (170)	VT (160–170)	6.8	(a) None	(a) VVI pacemaker; rate minimum to high
		(b) 157	24				(b) 7.4/10 (#1)	(b) recycle
							7.1/20 (#2)	Died, postop CHF/VT
9	LV	...	...	...	...	...	...	...
10	RVA	160	23	VT (273)	VT by AC (170)	6.7	7.4/18	BBB
11	RVA	173	30	VT (180)	VT (200)	8.7	8.0/14	BBB
12	RVA	160	25	VT (190)	VT (171)	7.3	7.8/20	BBB
13	LV	152	23.5	VT (158)	VT (300)	8.9	6.7/21	...
14	LV	160	23	VF	VF	7.5	7.2/17	...

* Joules = energy of first discharge; discharges 2, 3, 4 = 30 joules.
AC = alternating current; BBB = bundle branch block; CHF = congestive heart failure; LV = left ventricle; preop = preoperative; postop = postoperative; RVA = right ventricular apex; VF = ventricular fibrillation; VT = sustained ventricular tachycardia; VVI = demand ventricular pacemaker.

persisted, it was at a cycle length similar to that which was initially induced. Examination of the tracings from each case demonstrated that all IACD discharges occurred during the R wave of the VT.

In 2 cases (Patients 1 and 8), the IACD discharged while the patients were partially conscious. Both patients reported the sensation of a "thud" in the chest accompanied by the fleeting visual perception of colored lights. In neither case was the description that of intense pain or of electric shock. In all cases, at the time of IACD discharge, there was a noticable slight jerking motion of the torso.

The signal from the IACD bipolar rate lead provided a clear ventricular signal which averaged 15 ± 6 mV during sinus rhythm without evidence of atrial activity. During induction of the arrhythmias, discrete signals were again obtained which averaged 22 ± 8 mV. These direct-current signals were also placed on an FM tape recorder and later replayed through a bench model of the IACD. Patient rhythms were recorded from both the SVC-LV apex bipolar lead (former rate detector system) and from the present IACD ventricular bipolar lead. A square wave signal was used to indicate detection during sinus rhythm (Fig. 3) or VT (Fig. 4). In comparing these 2 systems, the SVC-LV apex bipole demonstrated some inaccuracies during both sinus rhythm and VT, whereas the rate detected through the IACD bipolar lead was much more accurate.

Follow-up results: After the hospitalization, which averaged 39 ± 23 (standard deviation) days, patients were returned to their referring physicians or to the Sudden Death Prevention Program Arrhythmia Clinic for periodic reevaluation and magnet testing of the IACD. In October 1982, the average follow-up period was 4 ± 2 months, and during this short period there was no documented out-of-hospital cardioversion.

In 1 patient (Patient 2), during routine follow-up, a nonfunctional unit was discovered and successfully replaced. Two patients (Patients 3 and 8) had bipolar ventricular demand pacemarkers implanted in addition to the IACD without interference being noted between the 2 devices.

Discussion

These results demonstrate the IACD capable of performing as both an R-wave synchronous cardioverter for VT and a defibrillator for VF. As shown in Table II, it converted VT at rates ranging from 160 to 300 beats/min. Where the initial discharge was ineffective, the rhythm was appropriately managed when the IACD recycled.

The accuracy of the R-wave synchronized rate counter using the ventricular bipolar catheter is illustrated in Figures 3 and 4. Compared with our former system, which employed an SVC-LV apex bipolar circuit[3] for rate detection, the IACD demonstrated greater accuracy during both sinus rhythm and VT. Occasional spurious discharges occurred with the earlier model,[13] particularly in patients with bundle branch block. In the present series, this was not observed during the limited follow-up period despite the fact that 5 patients had bundle branch block with QRS duration ≥120 ms (Table II).

This population had severe LV dysfunction as well as severe arrhythmias. Unfortunately this was reemphasized in 3 patients who died from heart failure. All had had heart failure preoperatively and only 1 (Patient 9) had received the IACD pulse generator which functioned appropriately. These patients are quite similar to our earlier group[3,13] except for the absence of nonischemic cardiomyopathy, usually found in approximately 25%.[14]

Based on the results of electrophysiologic study, this study confirms and extends our earlier reports that VT appears to be the major tachyarrhythmia initiating hypotensive symptoms. In the present series, VT was observed or induced in all cases except 1. While many rapid ventricular rhythms can be modified by therapy, these results suggest that VT occupies a preeminent role in initiating cardiac arrest. Nevertheless, 1 of our patients did have VF. Thus, any device used to automatically convert ventricular tachyarrhythmias must include the ability to manage both VT and VF.

The hospitalization time for patients who received the complete IACD system, including leads and pulse generator, was 39 ± 23 days. However, an arbitrary 30-day postoperative recovery period, before pulse

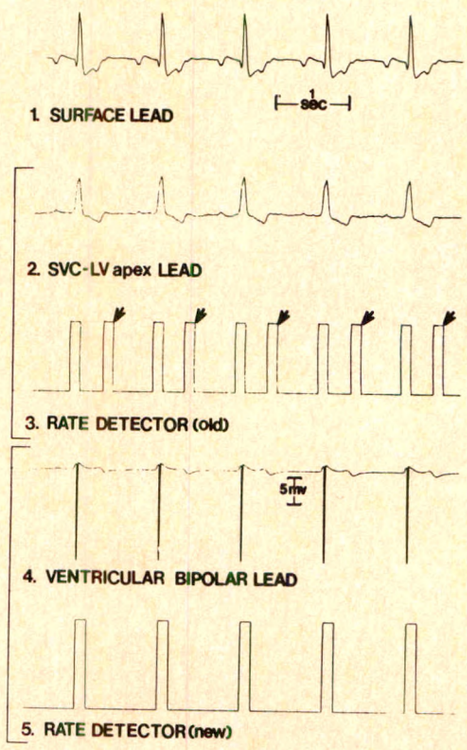

FIGURE 3. Recordings during sinus rhythm made at the time of IACD testing which show (**1**) surface lead V_1 with recordings from (**2**) the superior vena cava-left ventricular (SVC-LV) apex leads replayed through (**3**) the older (IAD) rate-detector circuit and recordings from (**4**) the ventricular bipolar lead replayed through (**5**) the present (IACD) rate detector circuit. Each detected signal and refractory period (panels 3 and 5) is represented by a square wave. The **arrows** (panel 3) demonstrate double rate-counting associated with voltage changes during the T wave (panel 2) when the older (superior vena cava-left ventricular apex) circuit is used. This counting error is avoided by using the ventricular bipolar signal (panel 4) and the new IACD rate circuitry (panel 5).

generator implant and testing, was required in any patient who underwent a ventriculotomy. This time should decrease as IACD surgery and pulse generator implantation can be performed as a single procedure.

The average follow-up period for the 11 patients was 4 ± 2 months. While all pulse generators were found to function properly during induced tachyarrhythmias and 1 spontaneous VT, there have been neither spontaneous out-of-hospital automatic conversions nor late deaths. Our longer experience (average 1.5 years) with the earlier defibrillator model has documented more than 75 automatic conversions and a significant increase in 1-year survival.[15]

Late hospital and follow-up complications appear to be relatively uncommon in these high-risk patients. One patient had a subclavian venous thrombosis, probably related to the SVC catheter (the first in 2.5 years) which completely resolved after heparin therapy. One patient had premature IACD battery depletion, which was replaced under local anesthesia. These events emphasize the importance of careful clinical follow-up after IACD implant.

While the IACD offers the potential for discontinuation of antiarrhythmic therapy, most patients appear to need some therapy to reduce the frequency of symptomatic events. Thus, the IACD is complementary to and supportive of other medical and surgical management. Two patients in this series required permanent (VVI) pacemakers. Both were bipolar and we were unable to demonstrate any interference with IACD performance. Nevertheless, pacemakers offer a potential source of interference: for example, rapid ventricular pacing beyond the IACD sensing period of 5 to 7 seconds or relatively large pacemaker pulses from atrioventricular sequential or unipolar systems which could lead to double rate counting.

The IACD offers several advantages over the earlier defibrillator. In addition to increased capability for management of VT, it permits noninvasive, audible verification of the R-wave sensing function, interrogation for the number of delivered pulses, and the ability to activate and deactivate the device. While it is easy to envision additional possibilities, such as programming and pacing, the IACD must not become so complex that effective use is precluded in a wide variety of clinical settings.

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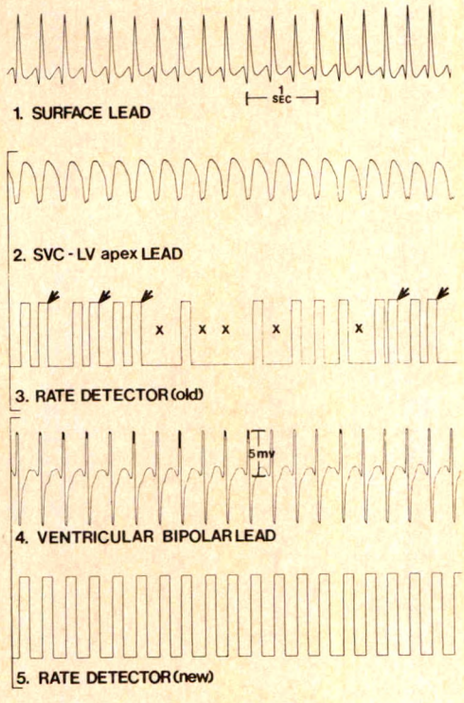

FIGURE 4. Recordings made during induced ventricular tachycardia at the time of IACD testing which show (**1**) surface lead V_1 with recordings from (**2**) the superior vena cava-left ventricular (SVC-LV) apex replayed through (**3**) the older (IAD) rate-detector circuitry and recordings from (**4**) the ventricular bipolar lead replayed through (**5**) the present (IACD) rate detector circuit. Each detected signal and refractory period (panels 3 and 4) is represented by a square wave. In panel 3 an **arrow** indicates double rate counting and an **X** indicates failure to detect a ventricular depolarization when the older (superior vena cava-left ventricular apex) circuit is used. These counting errors are avoided by using the ventricular bipolar signal (panel 4) and the new IACD rate circuit.

Addendum

Since submission of this manuscript we have documented 2 out-of-hospital IACD cardioversions in 2 different patients.

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Efficacy of Verapamil in Chronic, Recurrent Ventricular Tachycardia

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Verapamil, 0.25 mg/kg, was given to 24 patients with chronic, recurrent ventricular tachycardia (VT) whose clinical tachyarrhythmias were reproduced at electrophysiologic study. Seven patients (29%) responded acutely to verapamil: VT was not inducible in 5 and spontaneously terminated within 5 seconds of induction in 2 patients in whom it was previously sustained. Four of the 7 responders had no identifiable structural heart disease, and 3 had coronary artery disease. Responders were younger and had better left ventricular function than did nonresponders. Long-term therapy with verapamil, attempted in 5 of the 7 responders, was effective in 3, ineffective in 1, and of uncertain efficacy in 1. Verapamil therapy was discontinued because of worsened congestive heart failure in 2 patients.

The short-term efficacy of verapamil in these patients compares favorably with the efficacy of other antiarrhythmic agents against VT induction in patients with long-term, recurrent, drug-refractory VT. The short-term efficacy of verapamil correlated with its long-term efficacy. These observations provide preliminary evidence that verapamil may be useful in the treatment of some patients with recurrent VT. When standard drugs are not effective, verapamil should be given a trial, especially in young patients with good left ventricular function.

Previous reports regarding the efficacy of verapamil in chronic, recurrent ventricular tachyarrhythmias have dealt with small numbers of patients and have not generally been encouraging.[1–6] Nevertheless, it is reasonable to suspect that calcium-dependent phenomena underlie ventricular tachyarrhythmias in some patients. Triggered automaticity, a calcium-dependent phenomenon, has been demonstrated in vitro in human and subhuman primate cardiac tissues.[7,8] Circumstantial clinical evidence has supported the possibility that ventricular tachycardia (VT) is due to triggered automaticity in patients.[6,9] Slowly rising action potentials, possibly generated by slow inward calcium currents, have been demonstrated in diseased human ventricular myocardium.[10] Furthermore, recent evidence suggests that ischemia-induced ventricular tachyarrhythmias are suppressed by calcium antagonists and by reduced extracellular calcium ion concentration.[11] Thus, we examined the efficacy of verapamil as therapy for chronic, recurrent VT.

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Methods

Patients undergoing electrophysiologic study were consecutively selected to participate in this study if they had clinically recurrent VT, if their clinical arrhythmia was reproducibly inducible at electrophysiologic study, and if antiarrhythmic drugs, including beta-adrenergic antagonists, could be discontinued at least 24 hours before study. Patients were considered to have no structural heart disease when right and left heart pressure, left ventriculograms, coronary arteries, and 2-dimensional echocardiograms were normal.

VT was induced by ventricular extrastimulation according to a previously reported protocol.[12] VT was not inducible by rapid atrial pacing or atrial extrastimulation in any subject. Reliable inducibility of VT was established by reproduction 3 times of VT with rate, electrocardiographic QRS complex morphology, and duration similar to that of the clinical tachyarrhythmia. Repeated arrhythmia induction was not possible in the 3 patients who had continuous VT at the time of electrophysiologic study. Verapamil, 0.25 mg/kg, was then infused over a 15-minute period. Immediately at the end of infusion tachycardia induction was reattempted. After induction attempts were completed, blood was obtained through a femoral arterial catheter in 21 of the 24 patients for determination of the plasma concentrations of verapamil and norverapamil by a previously described liquid chromatographic technique.[13] If appropriate, long-term therapy with oral verapamil was instituted, and arrhythmia inducibility was again tested during stable oral therapy with verapamil.

Sustained and unsustained VT was defined as before.[12] Efficacy of verapamil was judged by the following criteria. At

TABLE I Characteristics of the Patients

Patients (n)	24
Age (yr)	56 ± 15
Male/female	22/2
Previous myocardial infarction (n)	16
Cardiomyopathy (n)	3
No structural heart disease	5
Cardiac index (liters/min/m^2)	2.5 ± 0.6
Left ventricular end-diastolic pressure (mm Hg)	14 ± 6
Sustained ventricular tachycardia (VT) (n)	18
Continuous VT (n)	3
Unsustained VT (n)	3
Continuous or >10 episodes of VT (n)	12
Two to 10 episodes of VT (n)	12
Previously ineffective drugs	3.5 ± 2.0

electrophysiologic study, the response to verapamil was considered complete if fewer than 6 ventricular repetitions could be induced after verapamil administration in patients with previously inducible sustained VT, or if fewer than 3 repetitions were induced in patients with previously unsustained VT. The response to verapamil at electrophysiologic study was partial if verapamil administration resulted in conversion of previously inducible sustained VT to inducible VT of less than 5 seconds' duration. Verapamil was considered effective during chronic oral therapy if a dose could be selected that resulted in absence of VT during electrocardiographic monitoring and absence of symptoms suggestive of VT recurrence. Therapy was initiated at 360 mg/day, and the dose was increased by 80 mg/day no more frequently than every 48 hours until tachyarrhythmia recurrence was prevented (Patients 1 and 2), a maximum safe dose was reached in subjects with heart failure (Patients 4 and 5), or a maximum dose of 8 mg/kg/day was reached (Patient 3). Each patient underwent at least 100 hours of electrocardiographic monitoring during chronic therapy with verapamil. Patients treated for longer than 6 weeks have undergone ambulatory monitoring every 3 months.

Means are expressed with standard deviations. Incidences were compared by 2 × 2 contingency table analysis with the significance of differences determined by a chi-square test with Yates' correction or by Fischer's exact test. Independent samples were compared by a 2-tailed unpaired *t* test or the Mann-Whitney rank-sum test.

Results

Twenty-four patients were studied (Table I). Although the majority of patients had coronary artery disease and previous myocardial infarction, 5 did not have structural heart disease identified by complete echocardiographic and angiographic studies. Eighteen patients had recurrent, sustained VT, 3 had continuous VT which persisted for days before electrophysiologic study, and 3 patients had recurrent, unsustained VT. VT was symptomatic in each patient, and each patient could accurately identify the presence of VT. Half of the patients had had more than 10 episodes or had continuous VT. On the average, each patient had failed to respond to 3.5 ± 2.0 individual antiarrhythmic drugs during clinical trial before electrophysiologic study because of recurrence of the clinical arrhythmia despite maximally tolerated doses.

At electrophysiologic study, 7 patients responded to verapamil, 2 of them having a partial response. Thus, verapamil prevented sustained arrhythmia induction in 29% of the patients. Characteristics of the responders are shown in Table II. None of them had received digitalis glycosides within 7 days of electrophysiologic study.

Responders were clinically different from nonresponders (Table III) in that they were younger and had better left ventricular function. Four patients without identifiable structural heart disease responded to verapamil and only 1 did not. There was no statistically significant difference between responders and nonresponders in the number of previously ineffective antiarrhythmic agents (2.9 ± 2.2 for responders, 3.7 ± 1.9 for nonresponders, $p > 0.4$), the nature of the VT (sustained, unsustained, or continuous), the rate of tachycardia, or the number of previous episodes. All 3 of the 7 responders to verapamil who received a clinical trial of propranolol failed to respond to it and an additional 1 still had inducible VT after receiving intravenous propranolol. The morphology of VT on 12-lead electrocardiography more frequently showed a pattern of right bundle branch block and left axis deviation in the responders (3 of 7 versus 3 of 17, $p = 0.36$).

Five patients received long-term oral therapy with verapamil (Table II). The 4 in whom stable maintenance therapy was achieved underwent repeat electrophysiologic study and remained classified as responders. Two patients (Patients 1 and 2) were young men without structural heart disease whose ventricular tachyarrhythmias have been effectively suppressed for more than 1 year. Patient 3, who also had no structural

TABLE II Characteristics of Responders and Results of Therapy

Patient	Age (yr) & Sex	Structural Heart Disease	Nature of VT	NYHA Class	Acute Response	Long-Term Therapy: Dose (mg)	Duration (mo)	Effective	Reason for Discontinuation
1	31M	0	Continuous	1	Complete	400	19	+	...
2	23M	0	Sustained	1	Complete	480	18	+	...
3	47F	0	Unsustained	1	Complete	600	1.5	0	Inefficacy
4	35M	+ (CAD)	Continuous	4	Complete	360	1.5	+	CHF
5	63M	+ (CAD)	Sustained	2	Partial	480	0.5	±	CHF
6	58M	+ (CAD)	Sustained	3	Complete	...	...	...	...
7	25M	0	Sustained	1	Partial	...	...	...	...

CAD = coronary artery disease; CHF = congestive heart failure; NYHA Class = New York Heart Association functional class; VT = ventricular tachycardia.

TABLE III Differences Between Responders and Nonresponders

	Responders	Non-responders	P Value
Patients (n)	7	17	...
Age (yr)	40 ± 15	62 ± 35	<0.001
Cardiac index (liters/min/m^2)	3.2 ± 0.4	2.3 ± 0.5	<0.001
LV end-diastolic pressure (mm Hg)	10 ± 4	15 ± 6	<0.001
Structural heart disease (n)	3	16	<0.018

LV = left ventricular.

heart disease, had recurrence of tachycardia on a maximum verapamil dose of 600 mg/day. In the last 2 patients (Patients 4 and 5), VT did not recur during maximal doses of verapamil, but the drug had to be discontinued in both because it significantly worsened preexisting congestive heart failure. In Patient 5 the duration of oral verapamil therapy was too short to assess its efficacy. Two responders (Patients 6 and 7) did not receive chronic oral therapy. One (Patient 7) had a partial response to verapamil, but ultimately had a complete response to imipramine at electrophysiologic study. The other underwent surgery for the arrhythmia.

Discussion

Verapamil is only rarely used to treat chronic, recurrent ventricular tachyarrhythmias because low efficacy rates have been reported in a few small series.[1–3] In these studies smaller doses (10 mg intravenously) than we used were given during ongoing VT. We are aware of only 1 study in which arrhythmia induction was included in the assessment of verapamil efficacy.[4] However, in that study, once again, only 10 mg were given to each of the 8 patients and only during established VT which was terminated by verapamil in only 1 patient. Our study differs from these in that a larger dose of verapamil was used (0.25 mg/kg, 18.5 ± 2.8 mg/patient), arrhythmia induction was used to test drug efficacy, and chronic therapy was attempted. McKenna et al[14] assessed chronic efficacy in 13 patients with hypertrophic cardiomyopathy and predominantly asymptomatic, unsustained VT (maximum duration 27 beats). Although verapamil did not appear effective, the patient population in that study is considerably different from ours.

The efficacy of verapamil in this study (29%) compares well with that of other individual antiarrhythmic agents assessed in our electrophysiology laboratory.[15] The most effective agents used in our laboratory, quinidine, procainamide, and propranolol, have completely or partially prevented VT induction, as defined herein, in 27 of 85 (32%), 17 of 52 (33%), and 5 of 17 (29%) trials, respectively. The overall incidence of individual antiarrhythmic drug efficacy in 405 trials in our laboratory is only 25%.[15] The mean age, indexes of left ventricular function, and incidence of normal heart structure of the 24 patients in this study do not differ from those of other patients evaluated in our laboratory.[15] Thus, our results suggest the possibility that verapamil is as effective as standard antiarrhythmic agents in the treatment of chronic, recurrent, medically refractory VT. This possibility requires confirmation in a larger group of patients. Patients who responded were younger, had better left ventricular function, and more frequently had no structural heart disease compared with nonresponders.

A previous case report[5] suggested the possibility that VT with a surface electrocardiographic pattern of right bundle branch block and left axis deviation occurring in patients without identifiable structural heart disease might represent a specific syndrome responsive to therapy with verapamil. Only 1 of our 7 responders had both no structural heart disease and this electrocardiographic pattern during VT. Absence of this electrocardiographic pattern and presence of structural cardiac disease did not preclude a response to verapamil.

Wu et al[6] reported on 3 patients without organic heart disease who had VT inducible by exercise but not by ventricular extrastimulation, and who responded to intravenous verapamil. They concluded that afterdepolarizations, which are dependent on or modulated by calcium ion, might be responsible for their patients' arrhythmias. Of course, a response of VT to verapamil cannot be taken alone as direct evidence for a specific mechanism of arrhythmia. Although verapamil is a potent inhibitor of the slow inward current, it has additional electrophysiologic and cardiovascular effects. Verapamil alters outward currents,[16] and its (+)-isomer blocks the myocardial sodium channel.[17] In addition, verapamil reduces left ventricular afterload and preload, reduces myocardial contractility, dilates coronary vessels, and promotes reflex autonomic adjustments to its hypotensive effects. Any of these additional actions conceivably could influence the inducibility and spontaneous occurrence of VT. Nevertheless, a response to verapamil provides circumstantial evidence that the affected arrhythmia resulted directly or indirectly from oscillatory afterpotentials or calcium-dependent, slow response action potentials.

The possibility that coronary artery spasm was responsible for tachyarrhythmias in these patients cannot be excluded conclusively because coronary arteriography, showing patent, normal vessels, was performed during VT in only 1 of the 7 responders (Patient 1). However, none of them had clinical evidence suggesting spasm. Although 2 responders had coronary artery disease, they did not have angina pectoris immediately before, during, or after episodes of tachycardia. None demonstrated S-T segment elevation before onset or after termination of VT. Furthermore, inducibility of tachycardia by extrastimulation in these patients makes coronary artery spasm an unlikely cause, because ventricular pacing is not known to induce coronary artery spasm and it is unlikely that spontaneous, asymptomatic spasm occurred coincidentally during attempts at VT induction.

Our protocol design may have been faulty, in that it did not compensate for a possible delay in peak effect of verapamil.[18] Also, we did not perform chronic trials of oral verapamil in patients with continued arrhythmia

inducibility after intravenous verapamil. We did not evaluate smaller doses of verapamil. The large intravenous and oral doses we used may have increased the incidence of heart failure. These design features may have reduced the potential efficacy of verapamil in this study.

We consider our findings on the efficacy of verapamil for treatment of VT preliminary because of the small number of patients in our study. In addition, only 2 of the original 24 subjects, both young and free of structural heart disease, continue on verapamil. However, until our findings can be confirmed or disaffirmed we recommend that verapamil be given a trial in patients for whom it is not contraindicated when other antiarrhythmic drugs have failed to control chronic, recurrent VT. Verapamil efficacy can be assessed at electrophysiologic study, as noninducibility of VT after intravenous verapamil correlated with arrhythmia nonrecurrence during chronic oral therapy. Our observations suggest that young patients with good left ventricular function and without identifiable structural heart disease are most likely to respond to verapamil.

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Electrophysiologic Effects of Lorcainide on the Accessory Pathway in the Wolff-Parkinson-White Syndrome

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The electrophysiologic effects of lorcainide, a class I antiarrhythmic agent with local anesthetic properties, were studied in 20 patients with the Wolff-Parkinson-White syndrome. After intravenous administration of lorcainide (2 mg/kg), the sinus cycle length decreased in all patients from 705 ± 117 to 636 ± 94 ms ($p < 0.001$). The atrioventricular conduction time lengthened from 84 ± 22 to 94 ± 22 ms ($p < 0.01$) and the QRS duration increased from 92 ± 19 to 120 ± 29 ms ($p < 0.001$). The effective refractory period of the atrium increased from 230 ± 27 to 243 ± 35 ms ($p < 0.05$), whereas the ventricular refractoriness was unaffected. Retrograde conduction over the accessory pathway was blocked in 5 of 18 patients after lorcainide; in the remaining 13 patients a prolongation from 107 ± 32 to 162 ± 57 ms ($p < 0.001$) was found. Anterograde conduction over the accessory pathway was blocked in 6 patients, and in all other patients it increased considerably. Circus movement tachycardia could be induced in 14 patients before and in 10 patients after the drug. The shortest R-R interval during tachycardia lengthened from 326 ± 40 to 364 ± 67 ms ($p < 0.05$). The tachycardia zone was unaffected by lorcainide. In 15 patients atrial fibrillation was induced. After lorcainide anterograde conduction during atrial fibrillation was blocked ($n = 5$). The shortest R-R interval over the accessory pathway during induced atrial fibrillation increased from 228 ± 35 to 304 ± 103 ms ($p < 0.05$). Intravenous administration of lorcainide produced a pronounced negative dromotropic effect on the conduction properties of the accessory pathway. Lorcainide appears to be a promising new antiarrhythmic agent in patients with the Wolff-Parkinson-White syndrome.

Lorcainide, a class I antiarrhythmic agent with local anesthetic properties, was recently introduced into antiarrhythmic therapy in Europe and is currently under investigation in the United States.[1] In clinical studies the drug was found effective against premature ventricular contractions and ventricular tachycardia.[2–8] Lorcainide has a disappearance half-life of 7 to 9 hours and is well absorbed under chronic oral therapy with a saturable presystemic elimination.[9] Initial electrophysiologic studies showed the drug to be useful in patients with the Wolff-Parkinson-White (WPW) syndrome and circus movement tachycardia.[10–12] This study substantiates the electrophysiologic effects of this agent on the accessory pathway in patients with the WPW syndrome.

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Material and Methods

Twenty patients (15 men and 5 women) aged 18 to 68 years (mean 39) were studied. Routine electrophysiologic investigations were performed because of unexplained supraventricular tachycardia in 4 patients and reciprocating tachycardias with known WPW syndrome in 14 patients. Two patients had a history of atrial fibrillation. Fourteen patients had electrocardiographic evidence of type A (Cases 1, 3, 7 to 10, 12 to 17, 19 and 20) and 4 patients type B WPW syndrome (Cases 2, 5, 6, and 18). In 2 patients a concealed left sided bypass tract was found, which conducted only in the retrograde direction (Cases 4 and 11). All studies were performed after informed written consent had been obtained. Cardioactive medications had been discontinued ≥72 hours before the beginning of the electrophysiologic study.

Electrophysiologic testing: Three quadripolar electrode catheters were usually introduced percutaneously through a left antecubital and right femoral vein and positioned under fluoroscopic control on the lateral wall of the high right atrium, into the apex of the right ventricle and in the region of the bundle of His. In those patients with a left-sided bypass tract, the high right atrial catheter was moved into the coronary

TABLE I Electrophysiologic Findings Before and After Administration of Lorcainide

Pt	CL (ms)	SCL (ms)	A-H (ms)	H-V (ms)	QRS (ms)	ERP_{Atr} (ms)	ERP_{Ventr} (ms)	ERP-ACC (ms) Ante	ERP-ACC (ms) Retro	Echo Zone (ms) Ante	Echo Zone (ms) Retro	VA (ms)	CL-CMT (ms)	PCR (μg/ml)
1C	500	770	65	50	85	220	195	<230	260	60	40	125	310	...
L		670	70	70	100	220	200	280	280	...	40	220	360	0.82–0.31
2C	500	560	50	35	90	200	200	<250	260	...	...	60	...	...
L		530	70	35	95	220	205	280	300	...	...	60	...	0.33–0.18
3C	430	500	145	40	75	220	180	240	<210	...	...	130	410	...
L		500	160	55	80	260	190	280	240	..	...	180	430	0.43–0.20
4C	500	650	55	50	95	230	200	...	260	50	...	60	345	...
L		550	65	70	170*	250	240	...	†	...	...	†	...	0.48–0.26
5C	600	900	100	40	100	260	...	300	360	100	...	100	310	...
L		700	105	50	110	250	...	†	360	...	...	†	...	0.70–0.32
6C	550	760	70	...	80	270	250	300	260	...	...	110	390	...
L		600	75	...	110	310	240	340	<250	...	...	210	490	0.37–0.23
7C	500	680	85	...	85	200	210	<240	280	...	...	70	290	...
L		620	...	...	105	220	210	260	300	...	...	80	330	0.40–0.20
8C	430	600	85	40	110	210	200	<220	<210	...	...	75	280	...
L		530	90	55	150	190	190	240	240	40	30	140	320	0.5–0.35
9C	600	920	70	35	75	250	220	<270	<330	...	...	120	...	...
L		700	...	...	110	280	205	†	†	...	...	†	...	0.46–0.32
10C	600	660	75	...	80	260	210	<270	270	...	...	110	295	...
L		530	110	...	...	280	...	<290	†	...	...	†	...	...
11C	500	710	110	30	100	230	200	...	240	...	80	190	300	...
L		600	100	45	120	220	200	...	†	...	...	†	...	...
12C	500	600	95	35	120	210	210	250	<220	40	...	110	360	...
L		570	90	60	140	260	205	†	260	...	...	160	320	...
13C	500	800	90	45	95	255	220	330	...	...	...	...	...	...
L		760	95	55	125‡	...	240	†	...	...	...	...	...	...
14C	500	670	110	45	85	240	190	295	230	...	...	150	345	0.28L
L§		840	...	...	115	260	...	†	460	245	...	270	450	0.76NL
15C	500	800	90	45	...	255	215	<260	325	...	...	95	310	...
L		730	95	...	...	255	230	<260	†	...	...	†	...	...
16C	500	850	75	45	85	265	220	<270	240	...	...	120	345	...
L		730	80	65	110	270	225	†	340	...	...	160	...	...
17C	500	770	80	35	80	210	210	<215	<220	...	100	115	280	...
L		710	95	45	105	230	190	<240	<200	...	70	180	330	...
18C	550	740	65	40	75	240	230	...	...	...	...	...	...	...
L		700	95	45	105	230	250	...	...	...	...	...	...	0.33–0.26
19C	500	610	70	...	150	220	210	230	<210	...	...	80	...	...
L		600	90	55	200	...	210	270	230	...	40	150	300	...
20C	430	550	90	40	80	165	185	235	240	...	...	110	...	...
L		560	110	65	105	165	210	270	285	...	...	145	315	...

* Left bundle branch block.
† Blocked.
‡ Right bundle branch block.
§ Patient 14 was restudied under long-term oral lorcainide therapy.
Ante = anterograde; Atr = atrial; C = control; CL = cycle length; CL-CMT = cycle length of the circus movement tachycardia; ERP = effective refractory period; L = lorcainide; NL = nor-lorcainide; PCR = plasma concentration range of lorcainide and nor-lorcainide during the time of electrophysiologic testing; Retro = retrograde; SCL = sinus cycle length; VA = ventriculoatrial conduction time; Ventr = ventricular.

sinus. This allowed registration of the earliest atrial depolarization in the vicinity of the bypass tract during right ventricular stimulation. The intracardiac electrograms were simultaneously recorded with standard electrocardiographic leads I, aVF, and V_1 at a paper speed of 100 mm/s using filter setting of 70 Hz (Mingograph 6 channel, Siemens Elema). Pacing and programmed stimuli at twice diastolic threshold strength and a duration of 1.8 ms were delivered by a Medtronic 5325 stimulator. Refractory periods of the right atrium, the right ventricle, the anterograde and retrograde conduction properties of the accessory pathway were determined using the extrastimulus technique with extrastimuli after every eighth driven beat. Pacing was performed from the right ventricular apex, the coronary sinus, and the right atrium. Rapid pacing was started with a cycle length of 500 to 600 ms and progressively shortened until second-degree atrioventricular or ventriculoatrial block had been observed or a cycle length of 200 ms was reached. Thereafter, the effective refractory period of the atrium and the right ventricle were evaluated by the extrastimulus technique. Identical cycle lengths were used before and after drug administration to avoid changes in excitability and refractoriness by variations in heart rate. During electrophysiologic testing, the sinus cycle length, the A-H and H-V intervals, and the QRS duration were measured before and after the drug had been given. In those patients in whom preexcitation was present during sinus rhythm, the H-V interval was measured when anterograde conduction over the atrioventricular node occurred during echo-beats or circus movement tachycardia. The ventriculoatrial conduction time over the accessory pathway was measured from the beginning of the earliest ventricular depolarization on either the His bundle electrogram or the right ventricular electrogram to the earliest atrial electrogram. For demonstrating relative changes in ventriculoatrial conduction, this procedure appears appropriate.

In 15 patients atrial fibrillation was induced by atrial stimulation up to a rate of 800 beats/min before and after lorcainide administration. The shortest R-R interval of ventricular activation over the accessory pathway was measured to examine the effect of the drug on the conduction properties of the accessory pathway during atrial fibrillation.

Drug protocol: After control measurements were completed, lorcainide was administered intravenously over a 5-minute infusion period in a dose of 2 mg/kg body weight in 19

patients. In 1 patient (Case 14) electrophysiologic testing was repeated during chronic oral therapy with lorcainide (100 mg 4 times daily). Repeated electrophysiologic measurements were made starting 7 to 10 minutes after intravenous administration, up to 30 minutes. Plasma levels of the drug were obtained in 11 patients, in 10 of them immediately after the end of the infusion period as well as 3, 7, 15, and 30 minutes later and in 1 patient during long-term oral therapy. Lorcainide was determined in the blood plasma of these patients using a specific gas chromatographic technique.[9]

Statistical methods: Data obtained before and after drug administration were compared by using Student's t test for paired data.

Results

Effect on impulse generation and conduction: Table I lists the pertinent electrophysiologic data of the patients studied. The sinus cycle length decreased in all patients from a mean of 705 ± 117 to 636 ± 94 ms ($p < 0.001$). The atrioventricular conduction time increased from 84 ± 22 to 94 ± 22 ms ($p < 0.01$). The intraventricular conduction time lengthened from 41 ± 6 to 55 ± 10 ms ($p < 0.001$). Lorcainide caused a widening of the QRS complex from 92 ± 19 to 120 ± 29 ms ($p < 0.001$). In 2 patients bundle branch block developed (left in Case 4; right in Case 13). One patient (Case 19) demonstrated left bundle branch block before and after the drug. In 2 patients (Cases 10 and 15), QRS duration was difficult to assess because of varying degrees of preexcitation.

The effective refractory period of the atrium increased from 230 ± 27 to 243 ± 35 ms ($p < 0.05$). Lorcainide had no consistent effect on ventricular refractoriness (208 ± 16 to 214 ± 19 ms, difference not significant).

Effect on conduction properties of the accessory pathway: The ventriculoatrial conduction time over the accessory pathway was examined in 18 patients before and after drug administration. Two patients (Cases 13 and 18) showed conduction over the accessory pathway exclusively in an anterograde direction. After lorcainide, retrograde conduction was blocked in 5 patients, whereas in the remaining 13 patients ventriculoatrial conduction was prolonged from a mean of 107 ± 32 to 163 ± 57 ms ($p < 0.001$). An example is presented in Figure 1. A reciprocating tachycardia could be induced in 14 patients before and in 10 patients after lorcainide administration. In 2 patients (Cases 18 and 19) a circus movement tachycardia could be induced only after the drug had been given. The shortest R-R interval during tachycardia lengthened from a mean control value of 326 ± 40 to 364 ± 67 ms ($p < 0.05$) thereafter. No consistent effect of lorcainide on the tachycardia zone during atrial or ventricular stimulation was observed. During atrial stimulation, the tachycardia zone decreased in 4 patients and increased in 3 patients. Patient 14, who was receiving long-term oral therapy with lorcainide, had a considerable increase of the tachycardia zone up to 295 ms, while it was absent under control conditions. Despite this fact, the R-R interval of the tachycardia induced increased from 345 to 450 ms in this particular patient. During right ventricular stimulation the tachycardia zone decreased in 2 patients and increased in 2 other patients. Refractoriness of the accessory pathway in an anterograde and retrograde direction often could not be measured because the refractory periods of the atrium and of the right ventricle encroached on that of the accessory pathway. In 9 patients anterograde refractory periods of the bypass tracts were shorter than the effective refractory period of the atrium during the control period. After lorcainide administration, the anterograde refractory period of the accessory pathway remained shorter than the effective refractory period of the atrium in 3 of them. After drug administration the anterograde conduction of the accessory pathway was totally blocked in 6 patients. In the other patients, the effective refractory period of the accessory pathway increased considerably.

The retrograde refractoriness of the accessory pathway could not be measured in 6 patients during the control period and in 2 patients after drug administration because the effective refractory period of the right ventricle exceeded that of the bypass tract. After lorcainide the retrograde effective refractory period of the accessory pathway could not be measured in 5 patients in whom the conduction was blocked during the time of study. In the remaining patients a prolongation of the effective refractory period of the accessory pathway in a retrograde direction was found.

The ventricular rate after induced atrial fibrillation

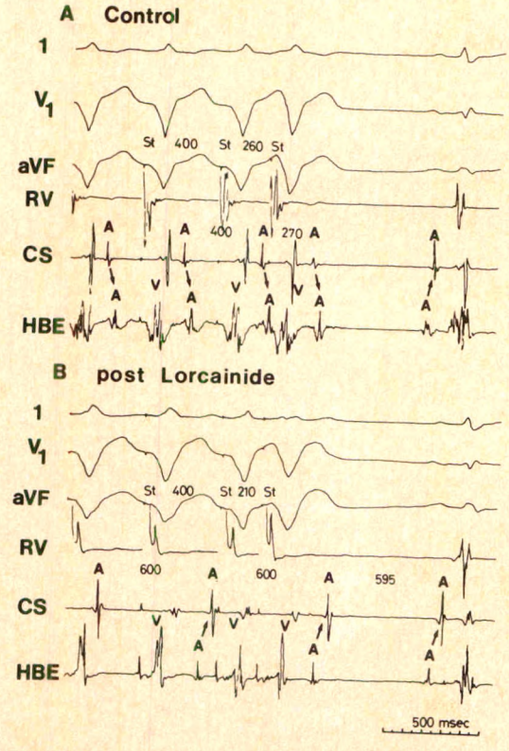

FIGURE 1. Effect of lorcainide on ventriculoatrial conduction over the accessory pathway (Case 10). Under control conditions the earliest atrial depolarization is detected in the coronary sinus during right ventricular (RV) stimulation, demonstrating a left atrial bypass tract. After lorcainide administration, ventriculoatrial conduction over the accessory pathway is blocked. CS = coronary sinus; HBE = His bundle electrogram; St = stimulus.

was assessed in 15 patients. In 1 patient (Case 4), anterograde conduction during atrial fibrillation occurred exclusively over the atrioventricular node. Another patient (Case 18) in whom anterograde conduction over the accessory pathway could not be observed during sinus rhythm and during atrial stimulation demonstrated QRS complexes with preexcitation intermittently during atrial fibrillation. The remaining patients showed anterograde conduction predominantly or exclusively over the accessory pathway. In these patients the anterograde conduction was either blocked (5 patients) or shifted to anterograde conduction predominantly over the atrioventricular node (Fig. 2). The shortest R-R interval over the accessory pathway increased from 228 ± 35 to 304 ± 103 ms ($p < 0.05$) (Fig. 3).

Plasma drug concentrations during the time of study: The plasma levels of lorcainide were measured in 10 patients during short-term administration and in Case 14 under long-term oral therapy with 100 mg lorcainide 4 times daily. The plasma concentration of lorcainide ranged from 0.46 to 0.16 μg/ml to 0.26 ± 0.06 μg/ml during the period of drug testing. Case 14 had a plasma level of 0.28 μg/ml, and the level of the N-dealcylated metabolite nor-lorcainide was 0.56 μg/ml. Nor-lorcainide levels were not detected after intravenous administration of the drug.

Side effects: No patient developed serious side effects from the drug. Fainting was reported by 2 patients. Two others complained of feeling hot and dizzy during the infusion. Two patients reported transient visual disturbances. One patient under chronic therapy with lorcainide complained of sweating, especially at night, and sleeplessness, which tended to diminish with ongoing therapy.

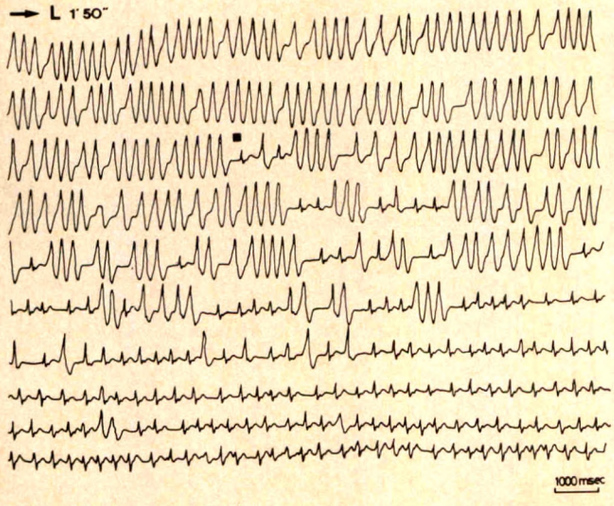

FIGURE 2. Effect of lorcainide on anterograde conduction over the accessory pathway after induced atrial fibrillation (Case 19). A continuous electrocardiogram registration during an ongoing lorcainide infusion depicted 1 minute and 50 seconds after the injection had begun (L 1'50") shows that anterograde conduction is shifted to antrioventricular conduction at the end of the infusion period exclusively.

Discussion

Effect on impulse generation and conduction: Until recently only a few electrophysiologic studies had been carried out to test the effects of lorcainide on electrical impulse generation and conduction in man. Our observation of increased sinus heart rate after intravenous administration of lorcainide in contrast to the prolongation of the atrioventricular, intraventricular, and intramyocardial conduction is consistent with findings in previous investigations. In these studies lorcainide decreased the R-R interval during sinus rhythm[10,13] or increased it only slightly.[12] This effect may be due in part to an anticholinergic effect of the drug.[10] The sinus node automaticity was depressed by the drug.[10,12] The atrioventricular and intraventricular conduction time was lengthened, as well as intramyocardial conduction.[10–13] The magnitude of these effects depends on the plasma concentration of the drug during oral therapy.[5]

Effect on the effective refractory period of the atrium and ventricle: A slight enhancement of the atrial refractoriness was noted. The effective refractory period of the right ventricle appeared to increase slightly. This change, however, was not statistically significant. Variable effects of the drug on the effective refractory period of the atrium and the ventricle have also been observed by other investigators.[12,13]

Effect on the conduction properties of the accessory pathway: Lorcainide caused a block in 6 of 17 patients in an anterograde direction and in 5 patients in a retrograde direction. Ventriculoatrial conduction was prolonged in all other patients in whom it could be measured. The negative dromotropic effect of the drug on the conduction properties of the accessory pathway was further substantiated by a prolongation of the cycle length of the circus movement tachycardia after drug administration.

Initial trials in a limited number of patients with the WPW syndrome have also shown that lorcainide can depress impulse conduction over the accessory pathway

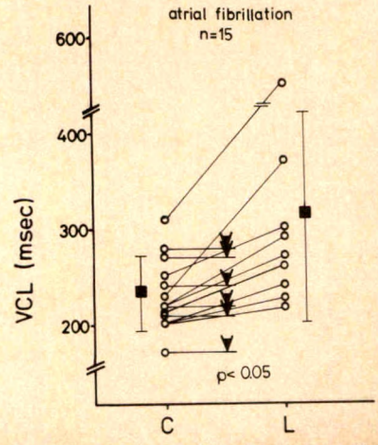

FIGURE 3. The ventricular cycle length (VCL) after induced atrial fibrillation increased in 9 patients and was blocked (**arrowheads**) in 6 patients. C = control; L = lorcainide.

in an anterograde and retrograde direction.[10,11,12] Similar to our findings in these studies, the refractory period of the accessory pathway was found prolonged in both directions.[11,12] Bär et al[11] reported that anterograde conduction over the accessory pathway was blocked after lorcainide administration in 8 of 11 patients. In a further study, anterograde conduction over the accessory pathway was blocked in 6 of 12 patients.[12] Retrograde conduction was blocked after the drug had been given in 2 of 11 patients.[11] In contrast, Manz et al[12] did not find a ventriculoatrial block in their patients.

A reciprocating tachycardia could be initiated in 14 of our patients before and in 10 after lorcainide. In 2 patients a circus movement tachycardia was only inducible after drug treatment. This finding is in accordance with observations of other investigators.[11,12] Pronounced prolongation of ventriculoatrial conduction over the accessory pathway by lorcainide with no or only little effect on the functional refractory period of the atrioventricular node[10] may have facilitated the initiation of tachycardia in these patients. The tachycardia zone was not systematically affected by the drug, which is consistent with findings by other workers.[11,12]

Patients with short refractory periods of the accessory pathway are prone to rapid ventricular rates if atrial fibrillation occurs. The marked negative dromotropic effect of lorcainide in a subgroup of patients characterized by a refractory period <270 ms deserves special consideration. Thirteen of our patients belonged to this subgroup.[14] Conduction was blocked in 3 of these patients (Cases 8, 11, and 15). In the remaining patients it was lengthened. The shortest R-R interval after induced atrial fibrillation was also prolonged after lorcainide.

The study was designed to investigate short-term effects of lorcainide on the accessory pathway. Therefore, conclusions cannot be drawn directly regarding the effects of the drug under long-term oral therapy. However, 1 patient who received long-term oral therapy with 400 mg/day of lorcainide demonstrated a favorable drug response. The accessory pathway was blocked in an anterograde direction, and the retrograde conduction properties of the pathway were considerably depressed. Despite these findings, a tachycardia zone of 245 ms was observed in a retrograde direction. Thus, in this patient the marked ventriculoatrial prolongation over the accessory pathway may have allowed the atrioventricular node to recover from refractoriness, resulting in a circus movement tachycardia. The tachycardia interval of the induced tachycardia was 450 ms. However, this was well tolerated by the patient.

Plasma drug concentrations determined in 11 of the 20 patients were comparable to the plasma concentrations found with long-term oral therapy.[5] It is possible that the electrophysiologic effects of lorcainide observed after intravenous drug administration were different from those which might be observed under chronic treatment. This may be due in part to the high plasma concentrations in the early distribution phase of lorcainide. On the other hand, it is well known that an active metabolite, nor-lorcainide, accumulates in the plasma in patients under long-term oral therapy,[5,8] which can enhance the electrophysiologic effects of the native compound.[5]

Clinical implications: The pronounced negative dromotropic effects of the drug on the accessory pathway, especially in patients with short refractory periods, might be of considerable value in the short-term treatment of circus movement tachycardia in patients with the WPW syndrome. The beneficial effect of lorcainide also seen in 1 patient under long-term oral therapy may indicate that this also holds true for long-term treatment. Further studies of long-term oral therapy are warranted to define the real therapeutic value of the drug in patients with the WPW syndrome.

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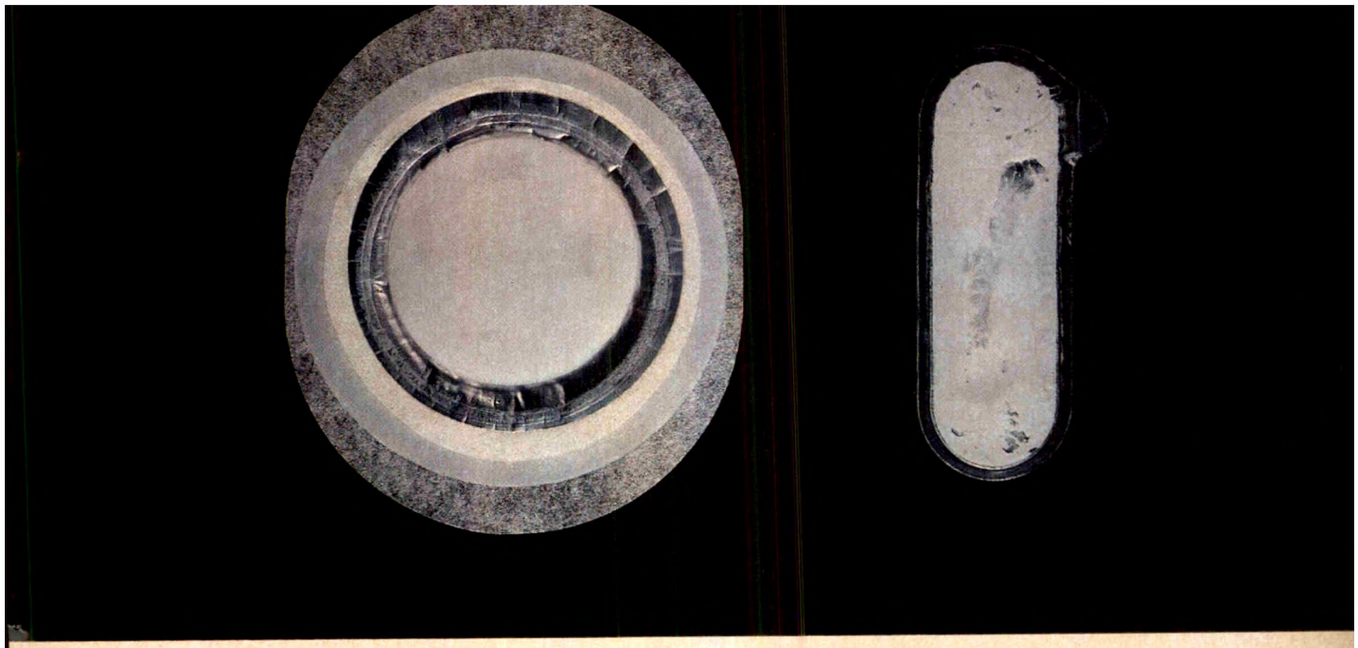

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INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

References

1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc. 01/83

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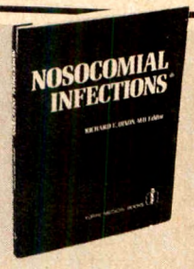

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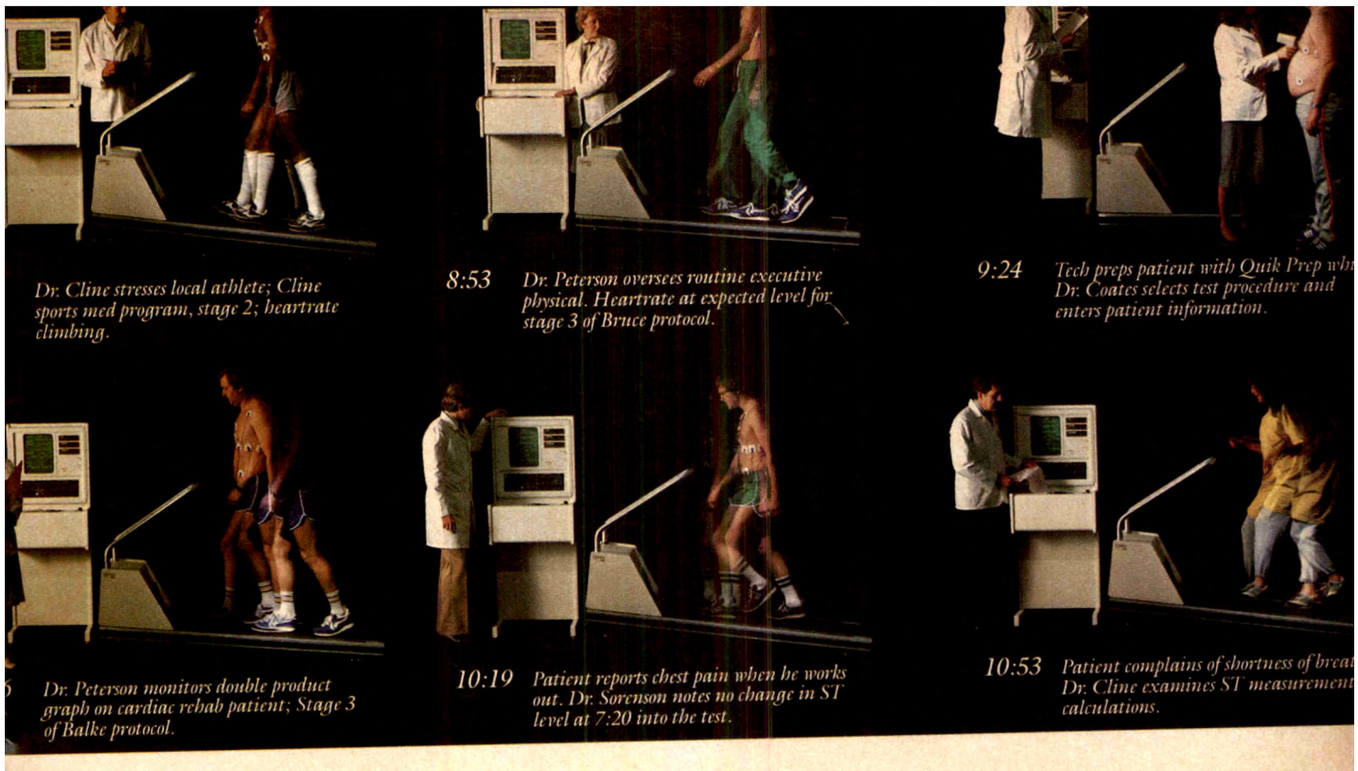

Dr. Cline stresses local athlete; Cline sports med program, stage 2; heartrate climbing.

8:53 *Dr. Peterson oversees routine executive physical. Heartrate at expected level for stage 3 of Bruce protocol.*

9:24 *Tech preps patient with Quik Prep wh Dr. Coates selects test procedure and enters patient information.*

Dr. Peterson monitors double product graph on cardiac rehab patient; Stage 3 of Balke protocol.

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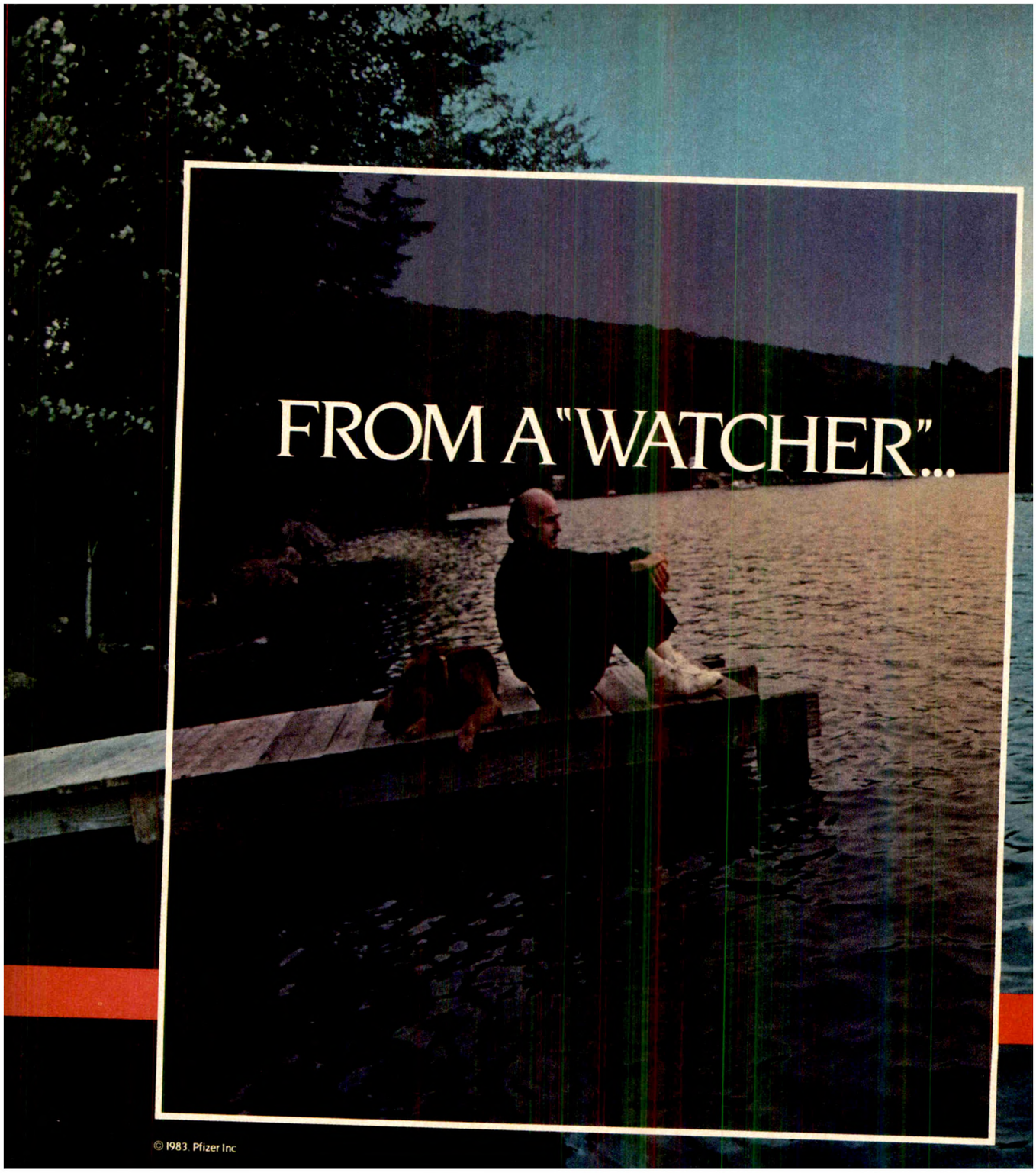
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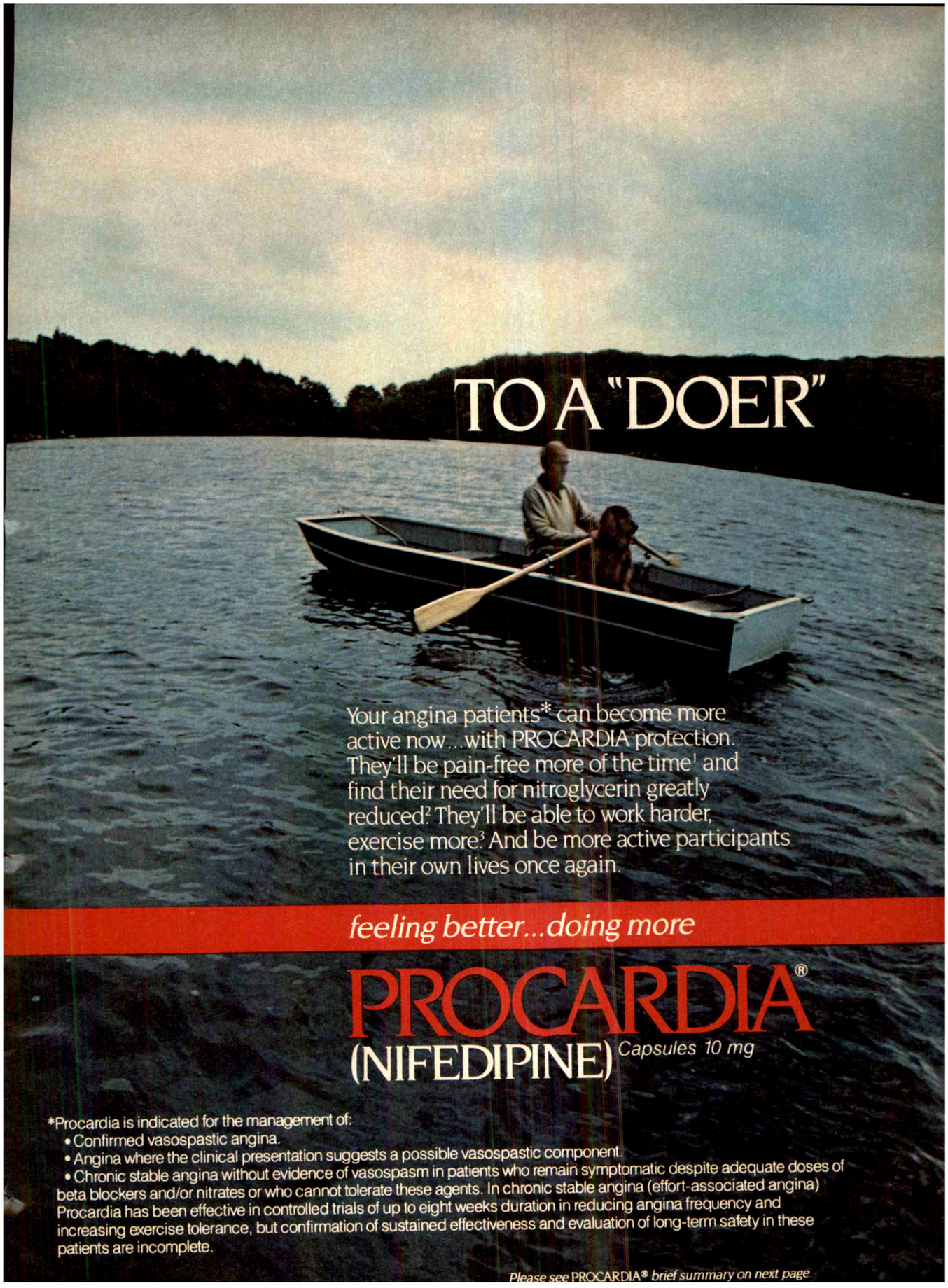
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–Usual effective dosage is 30-60 mg/day

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Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

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BRIEF SUMMARY
PROCARDIA® CAPSULES
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INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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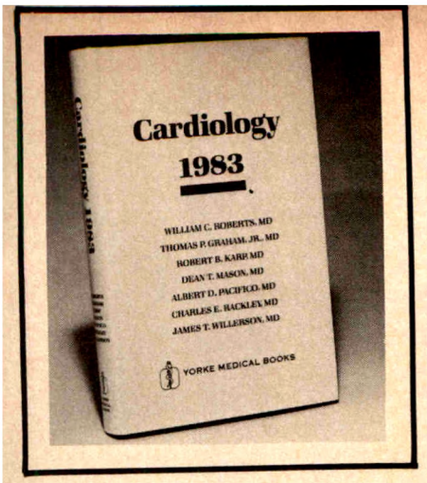

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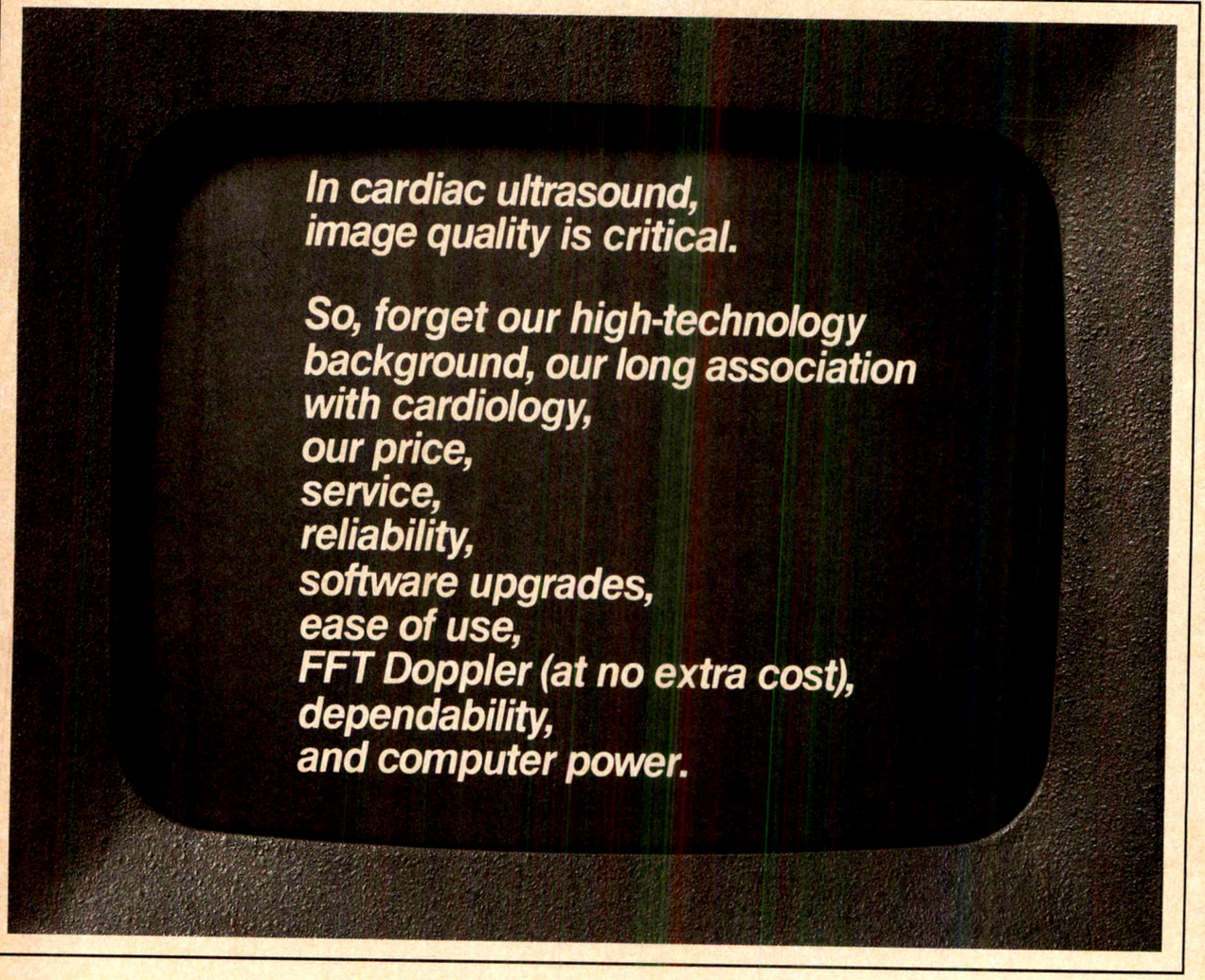

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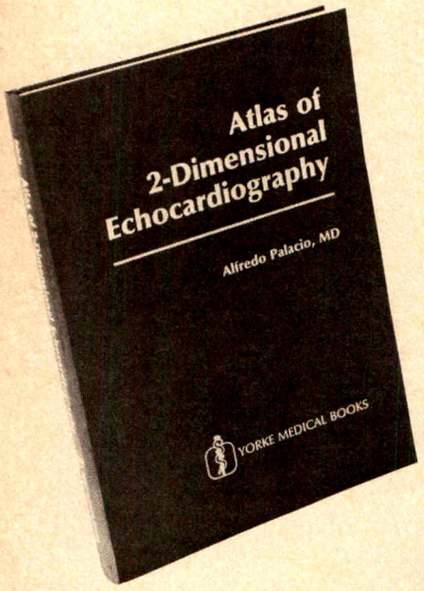

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Professor of Medicine, University of Massachusetts Medical School; Director, Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts
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Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Prescribing Information Tablets of 50 mg
Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (see **Warnings**)

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions Impaired Hepatic or Renal Function: The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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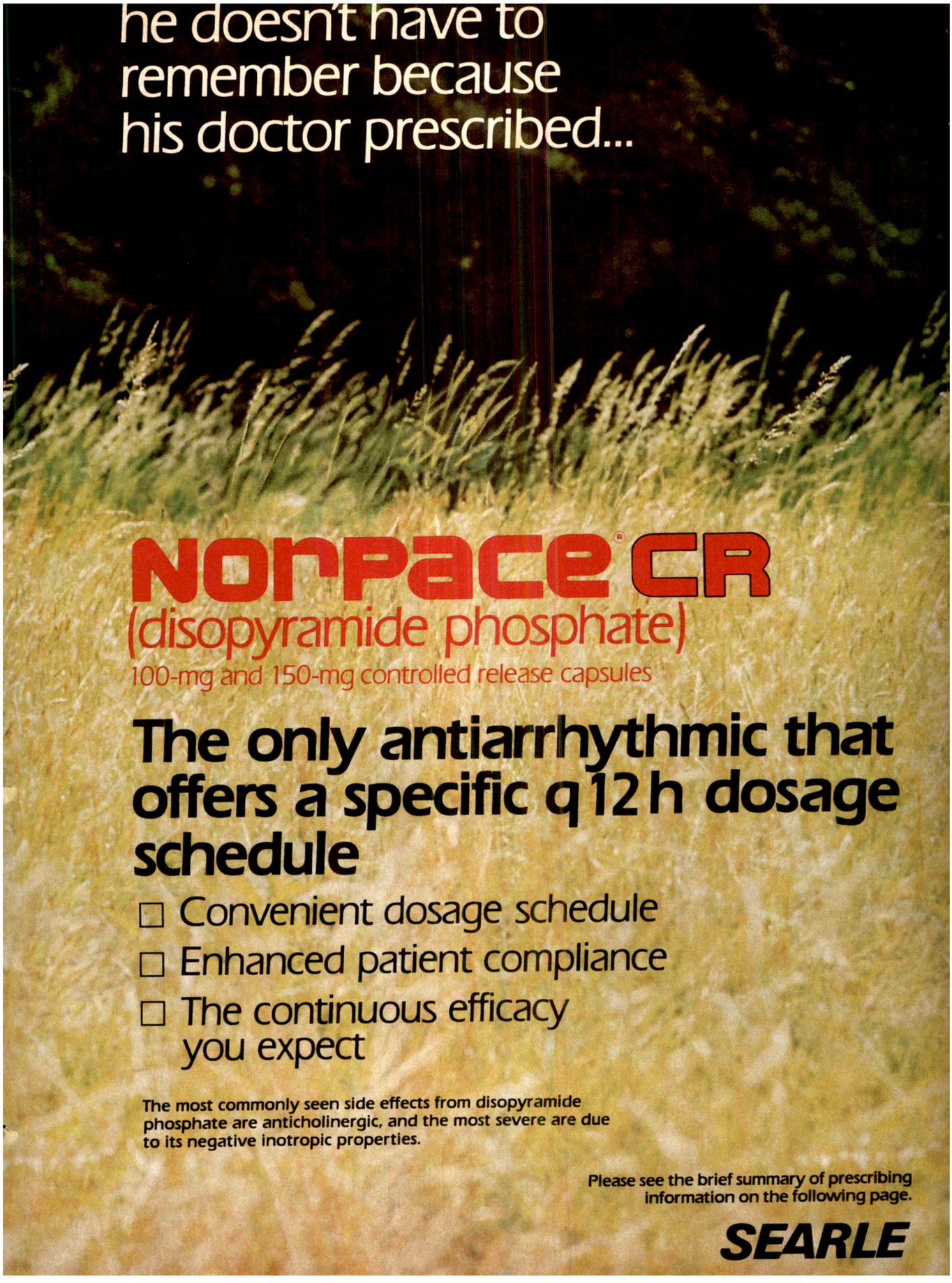
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Please see the brief summary of prescribing information on the following page.
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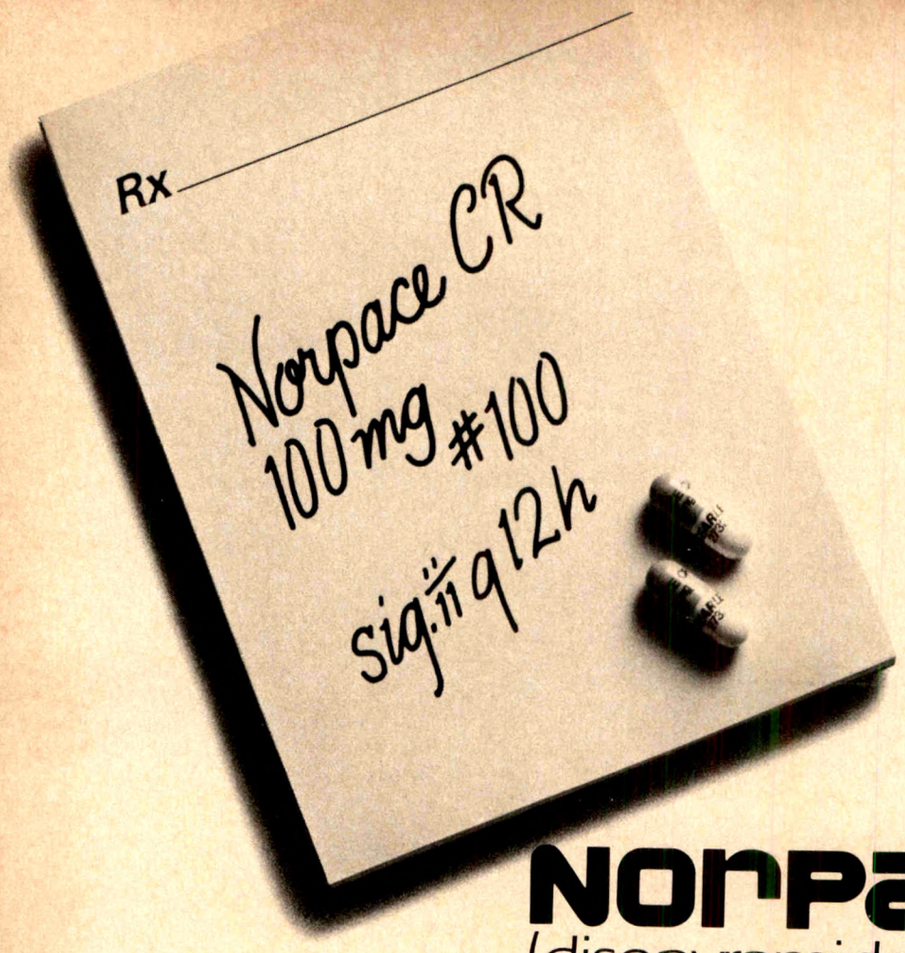

Norpace® CR

(disopyramide phosphate)

100-mg and 150-mg controlled release capsules

Before prescribing, please consult current complete prescribing information, a summary of which follows: **Indications:** For suppression and prevention of recurrence of the following cardiac arrhythmias: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs for overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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Electrophysiologic Testing in the Management of Patients With the Wolff-Parkinson-White Syndrome And Atrial Fibrillation

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Twenty patients with the Wolff-Parkinson-White (WPW) syndrome and 1 or more episodes of symptomatic atrial fibrillation (AF) due to rapid anterograde bypass tract conduction underwent electrophysiologic testing. The mean ventricular rate during spontaneous AF was 242 ± 56 beats/min (± standard deviation) and the shortest preexcited R-R interval was 194 ± 40 ms. Six patients underwent surgical bypass tract ablation and 14 were treated medically, based on the results of electropharmacologic testing. Over a mean follow-up period of 35 ± 19 months (± standard deviation), only 1 patient treated medically had a recurrence of minimally symptomatic AF. The successful chemoprophylaxis of symptomatic AF was associated with the inability to induce AF and atrioventricular reciprocating tachycardia during drug testing (7 patients) or with the induction of AF with a ventricular rate <200 beats/min and a shortest preexcited R-R interval of >250 ms (7 patients). Electrophysiologic testing can identify a subgroup of patients with WPW and AF in whom medical therapy is a suitable alternative to bypass tract ablation.

Patients with the Wolff-Parkinson-White syndrome (WPW) who have an episode of atrial fibrillation (AF) may have an extremely rapid ventricular rate due to rapid conduction through an atrioventricular bypass tract. In addition to causing symptoms due to hemodynamic compromise, such as syncope or weakness, the rapid ventricular rate that occurs during AF may also result in ventricular fibrillation.[1,2] One option available for the treatment of patients with WPW who have had an episode of AF associated with an extremely rapid ventricular rate is surgical ablation of the bypass tract.[3] This therapeutic option exposes the patient to the potential risks of open-heart surgery. Few data are available regarding the long-term results of medical therapy in patients with WPW and AF. We therefore examined the role of electrophysiologic testing in selecting patients with WPW and AF who may be appropriate candidates for medical therapy and in designing a drug regimen effective in preventing life-threatening episodes of AF.

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Methods

Twenty patients with WPW and at least 1 episode of symptomatic AF were referred to our institution between September 1976 and February 1982. A clinical profile of these patients is presented in Table I. Mean age was 35 ± 17 years (± standard deviation). Three patients had mitral valve prolapse, 1 had mitral regurgitation, and 1 had coronary heart disease; 15 patients had no structural heart disease. The patients had a mean of 2.1 ± 1.4 episodes of symptomatic AF over a period of 11 ± 12 months before referral to our institution. All patients had symptoms of syncope, presyncope, chest pain, or palpitations in association with AF. The mean ventricular rate during spontaneous episodes of AF in 18 patients was 242 ± 56 beats/min. The mean shortest preexcited R-R interval in 18 patients was 194 ± 40 ms. In 2 patients, AF with a rapid ventricular response degenerated into ventricular fibrillation after arrival at the hospital; in 1 patient, AF was observed on an electrocardiographic monitor before ventricular fibrillation but was not recorded. A third patient who had a previous history of AF had a cardiac arrest and was found by paramedics to be in ventricular fibrillation. Thus, in 2 patients a recording of AF was not available for analysis. Direct-current countershock was used to terminate AF or ventricular fibrillation on 1 to 4 occasions in 12 of 20 patients. The remaining 8 patients were treated emergently with intravenous procainamide or lidocaine. At the time that AF or ventricular fibrillation occurred, 10 patients were not being treated with any antiarrhythmic drug; 6 patients were being

TABLE I Clinical Profile

Patient	Age (yr) & Sex	Episodes of AF (n)	Onset of AF (Months Before Study)	Symptoms During AF	Ventricular Rate During AF (beats/min)	Minimum R-R (ms)*	DCC	Symptomatic AVRT
1	21M	3	30	Presyncope	180	200	0	...
2	21M	2	23	Presyncope	180	240	0	...
3	51F	1	1	Presyncope	300	180	1	+
4	31M	3	12	Presyncope	300	160	1	+
5	54M	3	8	Presyncope	280	160	3	...
6	39M	1	1	Presyncope	230	160	1	+
7	71M	1	1	Chest pain	190	240	0	+
8	21M	2	24	Presyncope	250	150	0	...
9	39M	1	6	Presyncope	210	240	0	+
10	59M	6	18	Presyncope	200	220	0	...
11	31M	1	5	Presyncope	240	180	1	...
12	50M	1	2	Palpitation	170	280	0	...
13	16F	1	6	Syncope	170	240	0	...
14	19M	2	24	Weakness	300	160	1	...
15	27F	1	1	CA†	ND	ND	1	+
16	31M	3	4	Palpitation, CA†	300	160	1	+
17	21M	1	1	Presyncope	300	160	1	...
18	18M	2	3	Presyncope, CA†	ND	ND	1	+
19	21M	1	1	Presyncope	330	160	1	+
20	58M	5	44	Presyncope	230	200	4	+
Mean	35.0	2.1	10.8	...	242	194	...	...
±SD	16.6	1.4	12.3	...	56	40	...	...

* Shortest preexcited R-R interval during atrial fibrillation.
† Cardiac arrest due to ventricular fibrillation.
AF = atrial fibrillation; AVRT = atrioventricular reciprocating tachycardia; CA = cardiac arrest; DCC = direct-current countershock; ND = not documented; SD = standard deviation.

treated with quinidine (0.8 to 1.2 g/day), 2 with procainamide (1.4 to 2.0 g/day), 2 with propranolol (80 to 160 mg/day), and 1 with digoxin (0.25 mg/day). In addition to having at least 1 documented episode of AF, 10 of 20 patients also had a 1 to 40-year history of recurrent palpitations of presyncope due to orthodromic atrioventricular reciprocating tachycardia. The bypass tract location was left-sided in 11 patients, right-sided in 2, and posteroseptal in 7.

After informed consent was obtained, an electrophysiologic study was performed with the patient in the fasting, nonsedated state. In 12 patients all antiarrhythmic drugs were discontinued at least 4 half-lives before the electrophysiologic study. At the time of referral to our institution, 8 patients had been treated empirically for at least 1 week with 1 or more antiarrhythmic drugs that were well tolerated. These patients were referred for evaluation of the efficacy of empiric therapy, and a baseline study was not performed.

Three quadripolar electrode catheters were inserted into a femoral vein by the Seldinger technique and positioned against the high lateral right atrium, across the tricuspid valve, and against the right ventricular apex. An additional quadripolar electrode catheter was inserted into a subclavian or antecubital vein and positioned in the coronary sinus. Surface leads V_1, I, and III and the high right atrial, His bundle, coronary sinus, and right ventricular electrograms were displayed on a VR-12 oscilloscope and recorded on an Electronics for Medicine recorder at a paper speed of 100 mm/s. Cardiac stimulation was performed with a programmable stimulator (Bloom, Narberth, Pennsylvania) at 2 to 3 times the diastolic threshold and with a pulse duration of 2 ms. Incremental right atrial, left atrial (coronary sinus), and right ventricular overdrive pacing was performed to a minimum paced cycle length of 250 ms. During overdrive pacing at a cycle length of 500 ms, single atrial or ventricular stimuli were introduced at 10 ms decrements throughout the respective diastolic cycles. Attempts were made to induce AF by repeated 15 second bursts of atrial overdrive pacing at cycle lengths of 200 to 40 ms (by 20 ms decrements), with a current strength of up to 10 mA. If the induced AF did not terminate spontaneously within 20 minutes, the patient was treated with either direct-current countershock (2 patients) or 100 to 1,000 mg of procainamide intravenously (10 patients) to terminate the AF. Nonsustained AF or reciprocating tachycardia was defined as AF or reciprocating tachycardia that terminated spontaneously within 30 seconds.

During drug testing, the following parameters were measured: anterograde effective refractory period (ERP) of the bypass tract, the shortest atrial overdrive cycle length at which there was a 1:1 conduction through the bypass tract, the inducibility and average rate of atrioventricular reciprocating tachycardia and AF, and the shortest cycle length between 2 consecutive preexcited complexes during AF. Whenever possible, at least a 2-minute duration of AF was analyzed to determine the average ventricular rate and the shortest prexcited R-R interval. In several patients, determination of the bypass tract ERP was limited by atrial refractoriness; in such cases the bypass tract ERP was expressed as being equal to or less than the atrial functional refractory period.

Drugs were chosen for testing depending upon each patient's history of drug intolerance and previous clinical drug trials. Electropharmacologic testing was performed immediately after the intravenous infusion of 1 or more of the following drugs: procainamide, 750 to 1,500 mg, propranolol, 0.2 mg/kg, or amiodarone, 10 mg/kg. One or more of the following drugs were tested after oral adminstration for at least 4 half-lives: procainamide, 1.5 to 6.0 g/day, quinidine, 1.2 to 2.0 g/day, disopyramide, 0.8 g/day, digoxin, 0.25 mg/day, propranolol, 160 mg/day, or metoprolol, 100 mg/day. Testing was performed with amiodarone after oral administration of 200 to 1,000 mg/day for 6 weeks because of the extended period of time required for this drug to attain its full therapeutic effect.[4]

Patients were selected to undergo surgical bypass tract ablation if sustained AF remained inducible during drug testing, with a mean ventricular rate ≥200 beats/min and a shortest preexcited R-R interval of ≤250 ms. The latter cri-

TABLE II Results of Electropharmacologic Testing and Follow-Up

Patient	Induced AF (Baseline) V Rate (beats/min)	Induced AF (Baseline) Minimum R-R* (ms)	Drug Regimen†	Induced AF (Drug Study) V Rate (beats/min)	Induced AF (Drug Study) Minimum R-R* (ms)	Months of Follow-Up	Recurrence of AF and RT
Patients Treated Medically							
1	165	260	P	120‡	320	13	...
2	190	280	P	NI	...	14	...
3	...	...	Q,N	NI	...	16	...
4	...	...	P,N	180‡	260	20	...
5	180	200	P	NI	...	21	...
6	160	210	Am	140	270	25	...
7	190	265	P,N	140	370	25	...
8	200	240	P	NI	...	25	...
9	...	...	Q,Dig,M	105	350	27	...
10	...	...	D	140‡	350	34	Rt X 2§
11	200	260	P	NI	...	50	AF X 1
12	...	...	Q	NI	...	69	...
13	...	...	Q,Pr	120	570	73	...
14	280	200	Q	NI	...	30	...
Patients Treated Surgically							
15	...	...	P,Pr	140	320	68	...
16	210	160	P	200	240	12	...
17	230	180	P,Am	210	250	12	...
18	210	240	P,D	200	210	44	...
19	...	...	P,Am	300	180	46	...
20	225	200	P	225	200	78	...

* Shortest preexcited R-R interval.
† Drug regimen most effective in suppressing or controlling the ventricular rate of induced atrial fibrillation and atrioventricular reciprocating tachycardia.
‡ Nonsustained (spontaneous termination within 30 seconds).
§ Noncompliant patient.
AF = atrial fibrillation; Am = amiodarone; D = disopyramide; Dig = digoxin; M = metoprolol; N = nadolol; NI = noninducible; P = procainamide; Pr = propranolol; Q = quinidine; RT = reciprocating tachycardia; V = ventricular.

terion was used because of an earlier study showing that patients with WPW who have had ventricular fibrillation have a shortest preexcited R-R interval of ≤250 ms during AF.[2] Bypass tract ablation was also recommended in 1 patient (Patient 15) who required open-heart surgery for correction of mitral regurgitation.

Patients not selected for surgical therapy were treated with drugs as guided by the results of electropharmacologic testing. Drug therapy was adjusted to yield serum drug levels that matched drug levels found to be successful in controlling or suppressing AF in the laboratory. All patients were followed by 1 of the authors or referring physicians and were seen at intervals of 3 to 4 months.

Values are expressed as mean ± 1 standard deviation. Statistical analyses were performed with Student's *t* test (paired or unpaired, as appropriate).

Results

Electropharmacologic testing and selection of long-term therapy (Table II): During drug testing in 5 patients, AF remained inducible and had a ventricular rate of ≥200 beats/min (mean 227 ± 42) and a shortest preexcited R-R interval of ≤250 ms (mean 216 ± 29). These patients were selected to undergo surgical bypass tract division. While being treated with procainamide and propranolol, Patient 15 had inducible AF with a ventricular rate of only 140 beats/min. She underwent bypass tract division at the time of mitral valve surgery for mitral regurgitation.

The remaining 14 patients were treated medically. Atrial fibrillation could not be induced in 7 of these patients during drug testing. Nonsustained AF was inducible in 3 patients and sustained AF was inducible in 4. In all 7 patients who had inducible AF, the mean ventricular rate during AF was <200 beats/min (mean 135 ± 24) and the shortest preexcited R-R was >250 ms (mean 356 ± 103).

Effects on bypass tract characteristics (Table III): In 8 of 15 patients in whom inducible AF was suppressed or controlled during drug testing and in 4 of 5 patients in whom it was not, a baseline electrophysiologic study was performed before drug testing. In the baseline state there was no significant difference between patients in whom inducible AF was suppressed or controlled and patients in whom the ventricular rate during induced AF was not controlled in the mean bypass tract ERP (≤287 ± 38 ms versus ≤250 ± 22 ms) or in the shortest atrial paced cycle length at which there was a 1:1 bypass tract conduction (316 ± 42 ms versus 275 ± 25 ms).

In the patients in whom inducible AF was suppressed or controlled, there was a significant increase in the bypass tract ERP during drug testing (≤287 ± 40 ms versus ≤321 ± 43 ms, $p < 0.05$); however, because determination of ERP was often limited by atrial refractoriness, a firm conclusion cannot be drawn regarding the ERP. There was no change in the shortest atrial paced cycle length at which there was a 1:1 bypass tract conduction before and after drug testing (316 ± 42 ms versus 325 ± 40 ms).

In the patients in whom the ventricular rate during induced AF was not controlled during drug testing,

TABLE III Effects of Electropharmacologic Testing on Bypass Tract Properties and Reciprocating Tachycardia

Patient	Baseline Study			Drug Study*		
	ERP of BT (ms)	1:1 BT Conduction† (ms)	CL of Orthodromic AVRT (ms)	ERP of BT (ms)	1:1 BT Conduction† (ms)	CL of Orthodromic AVRT (ms)
Patients Treated Medically						
1	270	300	340	240	275	NI
2	340	400	250	360	400	NI
3	310	350	240	≤360	300	NI
4	...	...	...	315	300	320‡
5	≤280	300	NI	≤330	300	NI
6	270	275	320	280	350	NI
7	335	325	410	350	325	NI
8	≤240	275	275	≤310	350	NI
9	...	...	...	350	350	NI
10	...	...	...	390	400	NI
11	...	...	...	300	350	NI
12	...	...	...	310	300	NI
13	...	...	...	360	400	400
14	250	300	NI	≤340	300	NI
Patients Treated Surgically						
15	...	...	...	350	350	450
16	≤230	300	310	270	300	350
17	≤250	250	275	≤280	275	300
18	280	275	360	320	NM	500
19	...	...	...	290	NM	NI
20	240	275	350	≤250	275	360

* See Table II for drug regimens tested.
† Shortest atrial paced cycle length at which there was 1:1 bypass tract conduction.
‡ Nonsustained (<30 seconds in duration).
AVRT = atrioventricular reciprocating tachycardia; BT = bypass tract; CL = cycle length; ERP = effective refractory period; NI = not inducible; NM = not measured, due to induction of atrial fibrillation by atrial pacing.

there was no significant change in the bypass tract ERP (≤250 ± 22 ms versus ≤280 ± 29 ms) or in the shortest atrial paced cycle length at which there was 1:1 bypass tract conduction (275 ± 25 ms versus 283 ± 14 ms) before and after drug testing, respectively.

During drug testing in the 5 patients in whom the ventricular rate during induced AF was not adequately controlled, the mean bypass tract ERP (≤282 ± 26 ms) was significantly shorter than in the 15 patients in whom suppression or control of AF was achieved (≤330 ± 38 ms, $p < 0.02$). The shortest atrial paced cycle length at which there was 1:1 bypass tract conduction was significantly shorter in the patients in whom induced AF was not controlled than in the patients in whom induced AF was controlled or suppressed (283 ± 14 ms versus 337 ± 41 ms, $p < 0.002$).

Effects on reciprocating tachycardia (Table III): Orthodromic reciprocating tachycardia remained inducible during drug testing in 4 of 5 patients in whom the ventricular rate during induced AF could not be controlled (tachycardia cycle length = 378 ± 86 ms). In contrast, among the 15 patients in whom control or suppression of inducible AF was achieved, sustained reciprocating tachycardia could not be induced by either atrial or ventricular pacing in 13 patients and was inducible in 2 (cycle length = 400 and 450 ms). Among the 6 patients who had inducible reciprocating tachycardia in the baseline state but not during drug testing, the site of block in the tachycardia circuit was the bypass tract in 5 patients and the atrioventricular node in 1.

Follow-up (Table III): Five of the 6 patients who underwent surgical bypass tract division have had no recurrence of symptomatic AF or reciprocating tachycardia over a mean follow-up period of 43 ± 31 months. In 1 patient, an attempt at surgical division of posteroseptal bypass tract was unsuccessful and reciprocating tachycardia recurred postoperatively. This patient was subsequently treated with amiodarone when it became available and has had no recurrence of symptomatic AF or reciprocating tachycardia over a 42-month follow-up period.

The mean follow-up period in the 14 patients treated medically was 32 ± 19 months. One patient had a spontaneous episode of palpitations due to AF with a mean ventricular rate of 150 beats/min; this was treated with intravenous procainamide. A second patient who admitted to erratic drug compliance had 2 episodes of palpitations due to a recurrence of orthodromic reciprocating tachycardia (140 beats/min). The other 12 patients have had no episodes of symptomatic AF or reciprocating tachycardia.

Spontaneous versus induced atrial fibrillation (Table II): Of the 12 patients who underwent a baseline study, in 2 patients orthodromic reciprocating tachycardia spontaneously degenerated into AF. Atrial fibrillation was induced by atrial overdrive pacing in the other 10 patients. The mean ventricular rate during induced AF in these 12 patients was 203 ± 32 beats/min, and the shortest preexcited R-R interval was 224 ± 38 ms.

In 11 patients in whom records of both spontaneous and induced AF were available, the ventricular rate during spontaneous AF, 244 ± 47 beats/min, was greater than during induced AF, 203 ± 34 beats/min ($p < 0.01$). The shortest preexcited R-R interval during spontaneous AF, 183 ± 33 ms, was shorter than during induced AF, 223 ± 40 ms ($p < 0.01$).

Atrial effective refractory period: The atrial ERP was measured in 12 patients before and during drug testing. All 12 patients had inducible AF during the baseline study. In 5 patients who no longer had inducible AF during drug testing, the atrial ERP increased after administration of drugs (232 ± 39 ms versus 298 ± 46 ms, $p < 0.01$). In 6 patients in whom AF remained inducible during drug testing, the atrial ERP also increased after administration of drugs, although to a lesser degree (229 ± 42 ms versus 256 ± 35 ms, $p < 0.05$).

Discussion

Our results suggest that a subset of patients who have WPW and potentially life-threatening AF can be treated safely and effectively with a drug regimen based on the results of electropharmacologic testing. Effective prophylaxis against the recurrence of symptomatic AF was associated with the inability to induce AF during the electropharmacologic testing or with the induction of AF with a ventricular rate <200 beats/min and a shortest preexcited R-R interval >250 ms.

In 2 patients in this series, orthodromic reciprocating tachycardia was observed to spontaneously degenerate into AF. This mechanism of AF in patients with WPW has been reported previously.[5–8] In such patients it may be necessary to suppress episodes of reciprocating tachycardia to prevent recurrences of AF. If induction of reciprocating tachycardia cannot be suppressed, a reduction in the rate of the tachycardia may be helpful in preventing a recurrence of AF, because the vulnerability to AF decreases as the atrial rate decreases.[9]

A previous study by Bauernfeind et al[10] also achieved successful medical therapy of patients with WPW and symptomatic AF. Among 8 patients with WPW who underwent electropharmacologic testing and were treated chronically with drugs that suppressed the induction of AF, over a mean follow-up period of 24 months, AF recurred only in 2 patients whose drug regimens were altered due to adverse effects. Our findings extend the observations of Bauernfeind et al by demonstrating that the complete suppression of AF induction during drug testing may not be necessary for successful long-term management of patients with WPW and AF. A good clinical response may also be obtained with drug therapy that does not suppress the induction of AF but that does decrease the ventricular rate during induced AF to <200 beats/min, lengthen the shortest preexcited R-R interval to >250 ms, and suppresses induction of reciprocating tachycardia.

There usually was no measurable prolongation in bypass tract refractoriness during drug testing when the baseline bypass tract ERP was <270 ms, as reported by Wellens et al.[11] However, because the determination of bypass tract ERP was often limited by atrial refractoriness, no firm conclusions can be drawn regarding the effects of drug testing on bypass tract ERP.

It is interesting to note that the mean ventricular rate during induced AF in the baseline state was significantly slower than during spontaneous AF in the same patients. Sympathetic tone would be expected to increase to a greater degree during a prolonged bout of spontaneous AF than during an episode of AF that is induced in a supine patient in the electrophysiology laboratory. Previous reports have shown that beta-adrenergic stimulation with isoproterenol may shorten the bypass tract anterograde ERP and result in an increased ventricular rate during AF.[12,13]

As reported by Bauernfeind et al,[10] suppression of inducible AF during drug testing was associated with significant prolongation of the atrial ERP. Although the atrial ERP was also lengthened during drug testing in patients who continued to have inducible AF, the magnitude of the change was less than in patients in whom the induction of AF was suppressed. An inadequate prolongation in the atrial ERP may be one factor accounting for the inability to suppress the induction of AF during drug testing.

Our study has the following limitations. (1) Ten of 20 patients had only 1 episode of symptomatic AF before undergoing electrophysiologic study. We must assume that without therapy, these patients would have had recurrent AF. (2) A baseline electrophysiologic study was not performed in 8 patients, 2 of whom did not have inducible AF during drug testing. In these 2 patients, we must assume that AF would have been inducible in the baseline state and that the inability to induce AF was due to a drug effect. (3) Bypass tract ablation was performed in all 5 patients in whom the ventricular rate during induced AF was not controlled. The long-term course of these patients had they been treated medically is not known. Therefore, it cannot be concluded that bypass tract ablation is necessary in such patients, since it is possible that drug therapy that suppresses ectopic beats may be effective in preventing life-threatening episodes of AF by eliminating the trigger for AF.

In conclusion, in patients who have WPW and episodes of AF with a rapid ventricular response, the decision to treat the patient medically or surgically should be individualized, based on the potential risks and benefits of each approach. The high success and low mortality rates associated with surgical division of bypass tracts (especially when the bypass tract is located in the free wall of the left or right ventricle[14]), together with elimination of the cost, inconvenience, and potential adverse effects of long-term drug therapy, argue in favor of this approach. However, the surgical approach exposes the patient to all the risks of open-heart surgery. We have demonstrated that electrophysiologic testing can identify a subgroup of patients with WPW and AF in whom medical therapy is a suitable alternative to surgical bypass tract ablation.

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Long-Term Recording of Monophasic Action Potentials From Human Endocardium

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In 36 patients undergoing routine cardiac catheterization, a new "contact electrode" catheter technique was used to record monophasic action potentials (MAPs) from right atrial and right and left ventricular endocardial sites without the application of suction. Although of smaller amplitude, typically ranging from 15 to 40 mV, and of different reversal ratio (33 ± 3%), MAP recordings closely resembled transmembrane action potentials in configuration and duration. Continuous MAP recordings of stable amplitude and, during regular pacing, of constant duration (±1% at 90% repolarization) could be made from the same endocardial site for test periods of 1 hour (n = 4), permitting direct evaluation of the effect of cycle length alterations on local myocardial repolarization. A linear relation was found between MAP duration and basic cycle length varying from 350 to 700 ms. These rate-dependent changes in MAP duration were caused by a change in the slow phase of repolarization (phase 2), whereas the slope of rapid repolarization (phase 3) was unaltered. Single premature MAPs or MAPs after a pause showed changes in both phases. No MAPs could be recorded in areas of infarcted, aneurysmal myocardium, indicating that local viable myocardium is a prerequisite for the generation of the monophasic signal. Thus, in human subjects this catheter permits safe, long-term recording of MAPs which, although of smaller amplitude than transmembrane action potentials, bear appropriate and predictable phase relations. Such recordings may be useful in evaluating changes in local myocardial electrical activity induced by pacing or resulting from myocardial disease, or both.

To examine the time course of local electrical activity under experimental conditions in which microelectrode recordings are difficult or impossible to make, such as in the vigorously beating in-situ heart, investigators have often used suction electrodes.[1–3] The signal obtained with suction electrodes is monophasic and, although of smaller amplitude, accurately reflects the onset of depolarization and the entire repolarization phase of transmembrane action potentials recorded from cells in the same vicinity.[3] Suction electrodes have also been used in human subjects,[4–6] but the potential for subendocardial damage and S-T segment elevation[5,7] has limited its clinical use to short recording periods of 2 minutes or less.[5–7] Because the shape and duration of the action potential vary from site to site in the heart,[8] longer recording time from a single endocardial site is needed to evaluate long-term MAP changes, such as heart rate effects over several basic cycle lengths or in response to pharmacologic interventions.

On the basis of earlier observations that MAPs can be obtained by simply bringing the exploring electrode into firm approximation with the myocardial surface,[9–11] we have developed a new "contact electrode" catheter that permits easy and safe long-term MAP recording from the human endocardium during routine cardiac catheterization.[12] This study (1) describes the characteristics of such MAP recordings from atrial and ventricular endocardium, (2) demonstrates the effects of abrupt and sustained cycle-length changes on MAP recordings from a single endocardial site, and (3) suggests that MAP mapping with this contact electrode technique may be useful in identifying abnormal myocardium.

Methods

Catheter design: The design is illustrated in Figure 1. Teflon® tubing and nonpolarizable electrodes made from cylindrical pellets of sintered silver-silver chloride are used. The tip electrode protrudes to form a smooth spherical surface 1 mm in diameter. The second, the reference electrode, is 0.5 mm in diameter 5 mm proximal to the tip and somewhat recessed so that contact is made only with the outer medium

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(blood) and not the endocardium. Unipolar catheters were also used, and contain only the tip electrode with a reference electrode placed in subcutaneous tissue remote from the heart, that is, at the site of catheter insertion. Total length of the catheters was 100 to 150 cm, and intravascular positioning was aided by a movable spring-steel guide wire.

Recording procedure: Before catheterization, electrodes were immersed in sterile 0.9% saline solution for 1 hour with leads short-circuited to balance half-cell potentials. This procedure ensured that no appreciable direct-current drift occurred during the course of the investigation. Diastolic baseline of intracavitary electrograms usually remained stable within ±1 mV during the entire recording time (1 to 3 hours), whereas stainless steel or platinum electrodes conventionally used in clinical electrophysiology may produce considerable baseline drift of up to 160 mV during the first 30 minutes (unpublished observation). After percutaneous catheter insertion by Seldinger technique and fluoroscopic positioning of the catheter within the heart, electrode leads were connected with sterile cables to a battery-powered differential preamplifier with an input impedance of 10^{11} Ω and a frequency range from direct current to 100 kHz (Grass Instruments, P16). The preamplified intracardiac signal and a standard precordial lead were displayed on a Tektronix storage oscilloscope and written out on a multichannel photographic recorder (Electronics for Medicine, VR-12). Data analyzed for MAP duration were recorded at 100 mm/s paper speed.

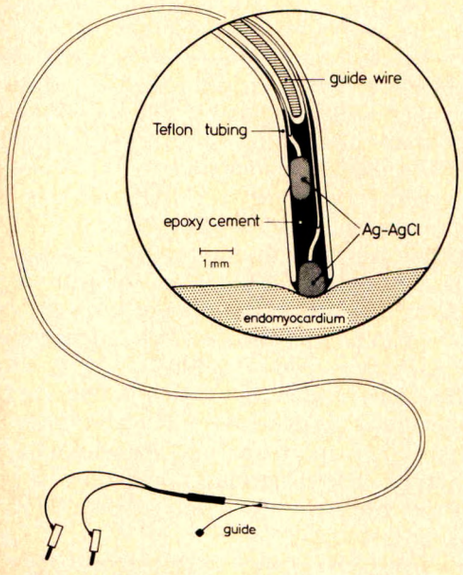

FIGURE 1. Design of contact electrode catheter (bipolar type). Ag-AgCl = silver-silver chloride.

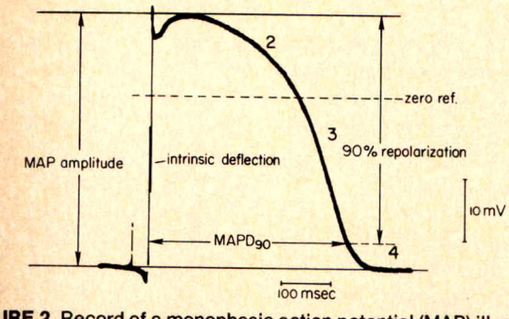

FIGURE 2. Record of a monophasic action potential (MAP) illustrating the methods of analysis. The plateau phase (phase 2), the phase of final repolarization (phase 3), and the diastolic baseline (phase 4) are labeled as conventional in intracellular recordings. The (retouched) upstroke of the MAP is much slower than that in intracellular recordings and is distorted by a notch that occurs at the time at which the intrinsic deflection[13] of the endocardial surface electrogram was recorded before the genesis of the monophasic signal. The superimposed intrinsic deflection was used as a reference marker for the beginning of the MAP, because its inscription accurately indicates the instant at which the excitation wave front passes the exploring electrode.[14,15] The MAP was negative during diastole and late systole and reversed its polarity during the early phase of activation with respect to zero reference which was derived from the isoelectric baseline of the intracavitary electrogram **(dashed horizontal line)**.

Characterization of the MAP: Figure 2 shows a typical MAP recording from a right ventricular endocardial site. The MAP amplitude was defined as the potential difference between the diastolic baseline and the crest of the plateau (phase 2). The duration of the MAP was measured as the time in milliseconds from the onset of local activation to the time of 90% repolarization ($MAPD_{90}$).

Electrical stimulation: To examine the effects of rate and rhythm on the MAP, recordings from a single endocardial site

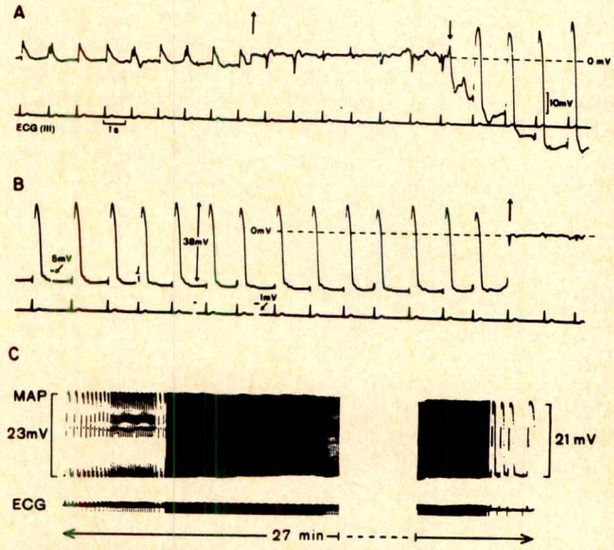

FIGURE 3. Monophasic action potential (MAP) recordings, intracardiac electrograms, and surface electrocardiogram (ECG) during catheter positioning in different locations within the right heart. At the beginning of the upper tracing (**A**), the electrode contacted the atrial endocardium close to the tricuspid valve, giving rise to MAPs of triangular shape typical of atrial muscle (notches appearing in some potentials are artifacts due to unstable endocardial contact). Withdrawal of the catheter from the endocardium (**arrow indicating upward**) resulted in a sudden return to the intracavitary signal. During the subsequent 7 heart beats the catheter was advanced through the tricuspid valve orifice into the apical region of the right ventricle, resulting in varying intracavitary electrograms. Firm approximation of the tip electrode to the endocardium (**downward arrow**) produced successively increasing negative potentials during diastole and positive displacements (reversal) during systole. Tracing **B** shows MAPs from a different right ventricular site. Withdrawal of the catheter from the endocardial surface is indicated by **upward arrow.** Note the absence of premature beats in these recordings. **C,** off-line recordings at varying tape and paper speeds, demonstrating MAP stability.

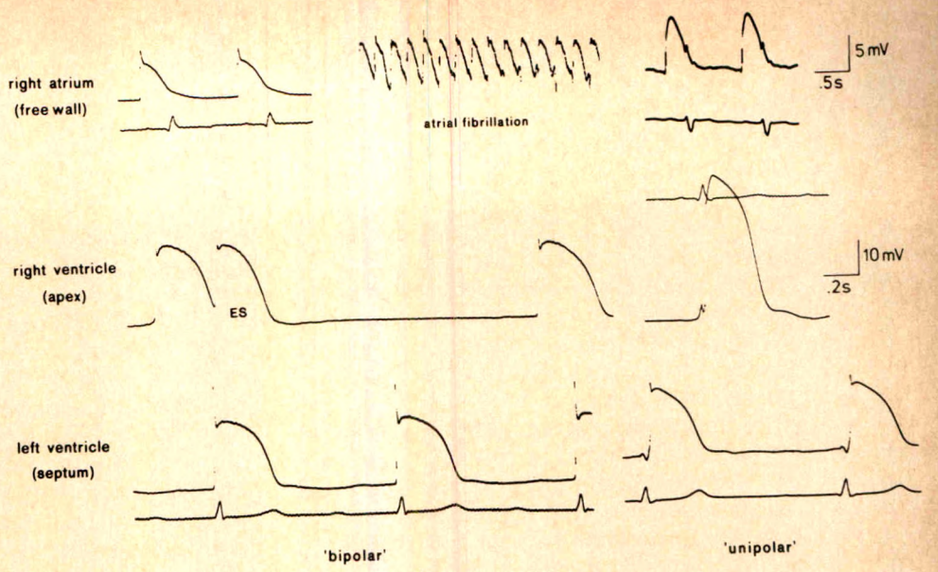

FIGURE 4. Monophasic action potentials recorded from various endocardial sites. Superimposed electrical activity (QRS) is minimized using a *bipolar* type of contact electrode catheter. ES indicates a premature beat followed by a compensatory pause.

were made during right atrial or ventricular pacing with rectangular stimuli of 1-ms duration and twice diastolic threshold strength.

Study population: Studies were carried out in 36 patients undergoing routine diagnostic cardiac angiography or electrophysiologic study. Informed consent was obtained from each patient, with the study design having been approved by the Committee on Human Investigations. Six patients had recordings from the right atrium, 32 from the right ventricle, and 5 from the left ventricle. Effects of heart rate alterations were evaluated in 8 patients, effects of atrial or ventricular extrasystoles, or both, in 12, and recordings from infarcted and noninfarcted areas of the same ventricle in 2. S-T segment changes did not occur and patient discomfort was not reported during the recordings.

Results

Recordings of MAPs: Adequate recordings were obtained in 34 of 36 patients. Contact of the electrode with the endocardium was indicated by the appearance of a fast biphasic deflection constituting the initial phase of the endocardial surface electrogram (Fig. 3). Pressing the electrode tip gently against the endocardium resulted in MAPs successively increasing in amplitude which reached a stable value within 2 to 6 beats. Although of smaller amplitude, the MAP shows close similarities in configuration to transmembrane action potentials. Withdrawal of the catheter from the endomyocardial wall resulted in a sudden return of the recorded potential to the isoelectric baseline. Premature beats sometimes occurred when the catheter was made to contact the endocardium but rarely resulted from the endocardial contact during the recording.

Stability of MAP recordings: Introduction of the catheter and establishment of stable endocardial contact were generally accomplished within a few minutes. Once stabilized, MAPs could be recorded continuously from the same endocardial site for periods of up to 3 hours without further manipulation of the catheter or readjustment of the electrode position. An example of the stability of the recorded MAP is demonstrated in Figure 3C in which a continuous record of 27 minutes is shown. As seen fluoroscopically, there was no movement of the catheter tip along the myocardial wall during the recording.

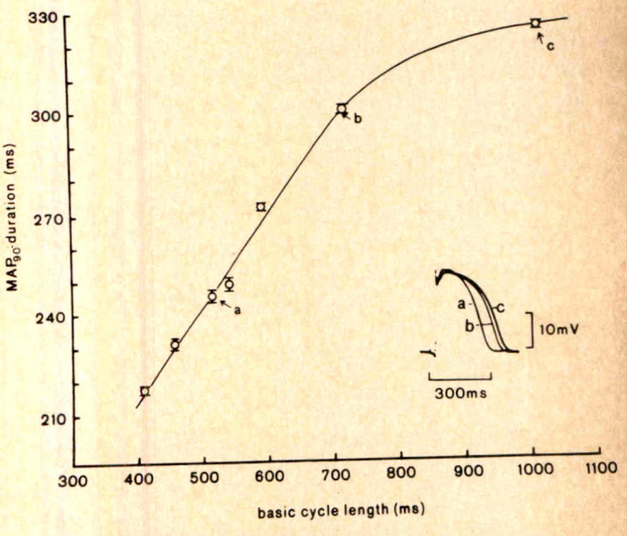

FIGURE 5. Effect of pacing at different basic cycle lengths on monophasic action potential configuration and duration at 90% repolarization (MAP_{90}) in a continuous record from a single right ventricular site in a patient who permitted atrial pacing at basic cycle lengths of up to 1,000 ms without escape beats. Data points and horizontal bars represent mean steady-state values (after 3 minutes of pacing) ±1 standard deviation. The curve was fitted by eye. Data points labeled a, b, and c refer to actual recordings as shown in the **inset.**

MAP recordings from different heart chambers: Typical examples of MAP recordings from the right atrium and both ventricles are shown in Figure 4. Similar to intracellular measurements, atrial MAPs are more triangular in shape because of a shorter phase 2 and a decreased slope of phase 3, as compared with MAPs recorded from ventricular endocardium.

Steady state recordings: At a single paced basic cycle length, the duration of the MAP at 90% repolarization ($MAPD_{90}$) was stable within ±1% for a test period of 60 minutes (n = 4). In Figure 5 a representative example of the effect of changes in basic cycle length on $MAPD_{90}$ is shown. With basic cycle lengths varying from 350 to 700 ms, $MAPD_{90}$ increased in linear fashion; at basic cycle lengths >600 to 700 ms, $MAPD_{90}$ approached a plateau. These steady-state cycle-length dependent changes in $MAPD_{90}$ were caused by changes in the duration of phase 2 whereas the slope of phase 3 was largely unchanged (Fig. 5, inset). Only at very long basic cycle lengths (≥1,000 ms) was a slight decrease in the slope of phase 3 observed.

Abrupt cycle length alterations: Changes in duration and repolarization contour of the MAP similar to those seen in transmembrane action potentials were observed in spontaneously arrhythmic beats or when the cycle length was abruptly altered by right atrial or ventricular pacing. Typical examples of premature and delayed right ventricular MAPs are shown in Figure 6. Premature depolarizations elicited within 100 ms after the effective refractory period were followed by MAPs of shorter duration because of an abbreviated phase 2 and a slightly steepened phase 3. However, those premature MAPs that were clearly separated from the preceding steady state response by a diastolic interval longer than 80 ms exhibited a prolonged phase 2 and a greater total duration. Relatively prolonged cycle lengths resulted in a greater total duration of the MAP because of a decreased slope of phase 3.

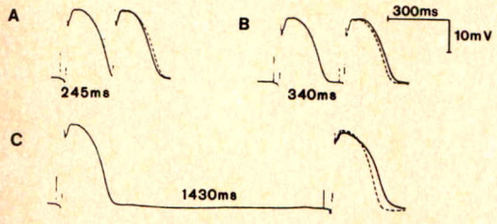

FIGURE 6. Changes in monophasic action potential duration and configuration after *abrupt* alteration in basic cycle length. Each set of recordings shows the last steady-state action potential at a cycle length of 428 ms, followed by an action potential at the indicated cycle length. The dotted recordings are superimposed reproductions of the steady-state action potential.

Amplitude and polarity of MAP recordings: Amplitudes of MAPs recorded from the right or left ventricular endocardium were comparable and usually ranged between 15 and 40 mV. MAPs recorded from the right atrium were considerably smaller and usually below 10 mV. The use of nonpolarizable electrodes in conjunction with direct-current recording made it possible to observe the magnitude of negative and positive potentials with respect to the isoelectric baseline of the intracavitary electrogram. With the exploring (tip) electrode connected to the positive input of the amplifier, a negative potential is recorded during diastole and a positive potential (reversal) during the initial part of systole (Fig. 3). As also seen in Figure 3, the reversal (positive displacement) increases with the total amplitude of the MAP. The ratio between MAP reversal and total amplitude was stable (33 ± 3%, n = 19) regardless of the total amplitude or the site from which the recording was made within the heart.

Effect of myocardial scarring on MAP recordings: In 2 patients with large left ventricular aneurysms demonstrated by cardiac angiography, recordings were carried out at several left ventricular sites (Fig. 7). At sites in which wall motion appeared relatively preserved, MAPs of >25 mV amplitude were recorded, whereas at the center of the aneurysm no MAP could be recorded, but rather only a signal similar to the intracavitary electrogram. At an intermediate location close to the area of preserved wall motion, small monophasic deflections were recorded (site 2, Fig. 7).

Discussion

This study shows that by using a specially designed contact electrode catheter, stable MAPs can be recorded from a single endocardial site continuously over prolonged periods of time. These MAP recordings resemble intracellular recordings in showing similar configuration

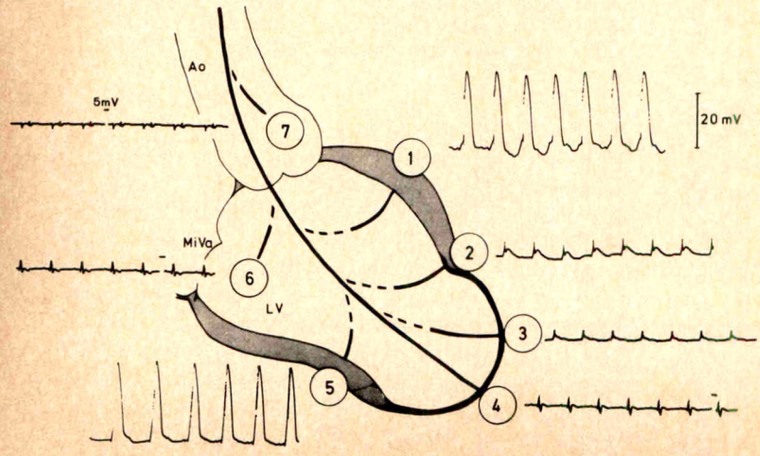

FIGURE 7. Monophasic action potential (MAP) recordings (unipolar type of catheter) from various left ventricular (LV) sites in a patient with 1-year-old anteroapical aneurysm (schematically depicted). Positions 6 and 7 show electrograms recorded from within the LV cavity and ascending aorta, respectively. Positions 1 and 5 indicate normally contracting wall segments. Positions 3 and 4 indicate recordings from the akinetic segment and show no true MAPs, rather only intracavitary signals. Position 2 is in the border zone of the aneurysm and shows small monophasic deflections.

and duration which change appropriately in response to abrupt or sustained cycle-length alterations. Prolongation of phase 2 and steepening of phase 3 in premature action potentials and opposite changes after single, relatively prolonged intervals (Fig. 6) have previously been observed in intracellular recordings from isolated dog,[16] rabbit,[17] pig,[18] and human[19] ventricular myocardium. Changes in MAP duration and configuration with different *basic* cycle lengths were due mainly to a change in plateau duration while the slope of phase 3 remained unaltered. This and the finding that the steady-state interval-duration relation of the MAP was closely linear over the physiologic range and flattened at long cycle lengths (Fig. 5) are also similar to previous, intracellular measurements from excised canine[20] and human ventricular muscle.[21]

Because the endocardium is rich in Purkinje fibers, it is possible that some recordings may be a composite of Purkinje and ventricular muscle fibers which mutually affect each other electronically. However, the cycle-length–dependent changes in MAP configuration shown in Figure 6 contrast with those reported for Purkinje fibers,[18] suggesting that these recordings represent mainly ventricular muscle activity.

Although the (relative) repolarization time course of the MAP appears to reflect that of intracellular measurements, the MAP does not contain information about the absolute magnitude of the transmembrane resting and action potential.[3] MAPs recorded with this technique from ventricular sites had amplitudes typically between 15 and 40 mV and, in contrast to intracellular measurements, were considerably smaller at atrial sites, rarely exceeding 10 mV. It is also important to note that the upstroke of the MAP signal has a lower rise velocity than do intracellular recordings and often shows shape irregularities (Fig. 2). These may result from the fact that the contact electrode is large and must record from a number of cells whose activity is somewhat dispersed in time and space. Irregularities in the upstroke of the MAP may also arise from nearby electrical activity associated with the excitation wave front.[3,15] Further distortion of the recordings may result from remote potentials (QRS complex and T wave) superimposed on the MAP. Such superimpositions are minimized by the close proximity of the recording electrodes and differential amplification (Fig. 4).

The extent to which the MAP reverses its polarity during activation has attracted much attention.[1–3,22–25] In suction electrode recordings the positive (systolic) potential is usually greater than the negative (diastolic) potential.[3,23,24] A lesser but still significant difference from intracellular measurements was found in our recordings in which the positive reversal was one third the total amplitude, regardless of the value of the latter or the site from which the recording was made. A similar and likewise uniform reversal ratio was described in an early analysis of MAPs which were also obtained by pressing an electrode onto the myocardial surface.[22]

Although this study in human subjects cannot define the exact mechanism underlying the genesis of the contact electrode MAP, the following theoretical concept conforms with the presented data. Pressure against the endocardium depolarizes a number of subendomyocardial cells to a degree that they no longer participate in regenerative depolarization and repolarization. During diastole, the local current flow resulting from the potential gradient between the depolarized area and the normal resting potential causes a negative potential at the recording site. During systole, the overshooting depolarization in normal cells reverses the potential gradient and thus the direction of current flow, and a positive potential is recorded. Under the existing volume conductor conditions,[15,26] the magnitude of local current flow, and therefore of the MAP, may be influenced by the number of cells depolarized by the tip electrode. In summary, the contact electrode likely creates an area of continuously diminished membrane potential which serves as a reference for the potential changes in adjacent cells. This reference need not be at zero potential, as cells affected by the electrode contact may maintain some resting potential, which may explain the observation that the reversal ratio of the MAP is greater than that in intracellular recordings.

The concept of the genesis of MAP just suggested herein explains why, in an area of scar, no MAPs could be recorded, but rather only remote electrical field changes generated by the entire heart, similar to an intracavitary electrogram (Fig. 7). Nonviable myocardium not only is devoid of a membrane potential but also is electrically uncoupled[27,28] and therefore cannot generate the current flow responsible for the MAP. However, electrical uncoupling and therefore the ability to record the extracellular potential may result from conditions other than cell death such as extremely high myoplasmic calcium concentration.[28]

Suction electrode recording requires sterile filling of the catheter with saline solution, manipulation with a suction pump, and other technical features[6] that make their clinical application cumbersome. More important, suction electrode catheters result in focal hemorrhage at the site of suction within a few minutes.[7] In contrast, no macroscopic damage to the subendocardium was seen in animal studies in which continuous contact electrode recording was performed for 30 minutes.[12,29] Furthermore, the stability of the contact electrode MAP over long recording periods may be considered indirect evidence that cellular alterations that lead to electrical uncoupling were minimal.

Thus, MAP recording by means of this specific method appears to be safe and can easily be performed during routine cardiac catheterization along with other electrophysiologic measurements and pharmacologic interventions.[30] A recent study in the animal model shows that MAPs recorded with this technique also provide a sensitive index of acute myocardial ischemia,[29] suggesting that endocardial MAP mapping may serve as a method not only for estimating normal cellular electrical activity but also for detecting electrophysiologically abnormal or nonviable myocardial areas.

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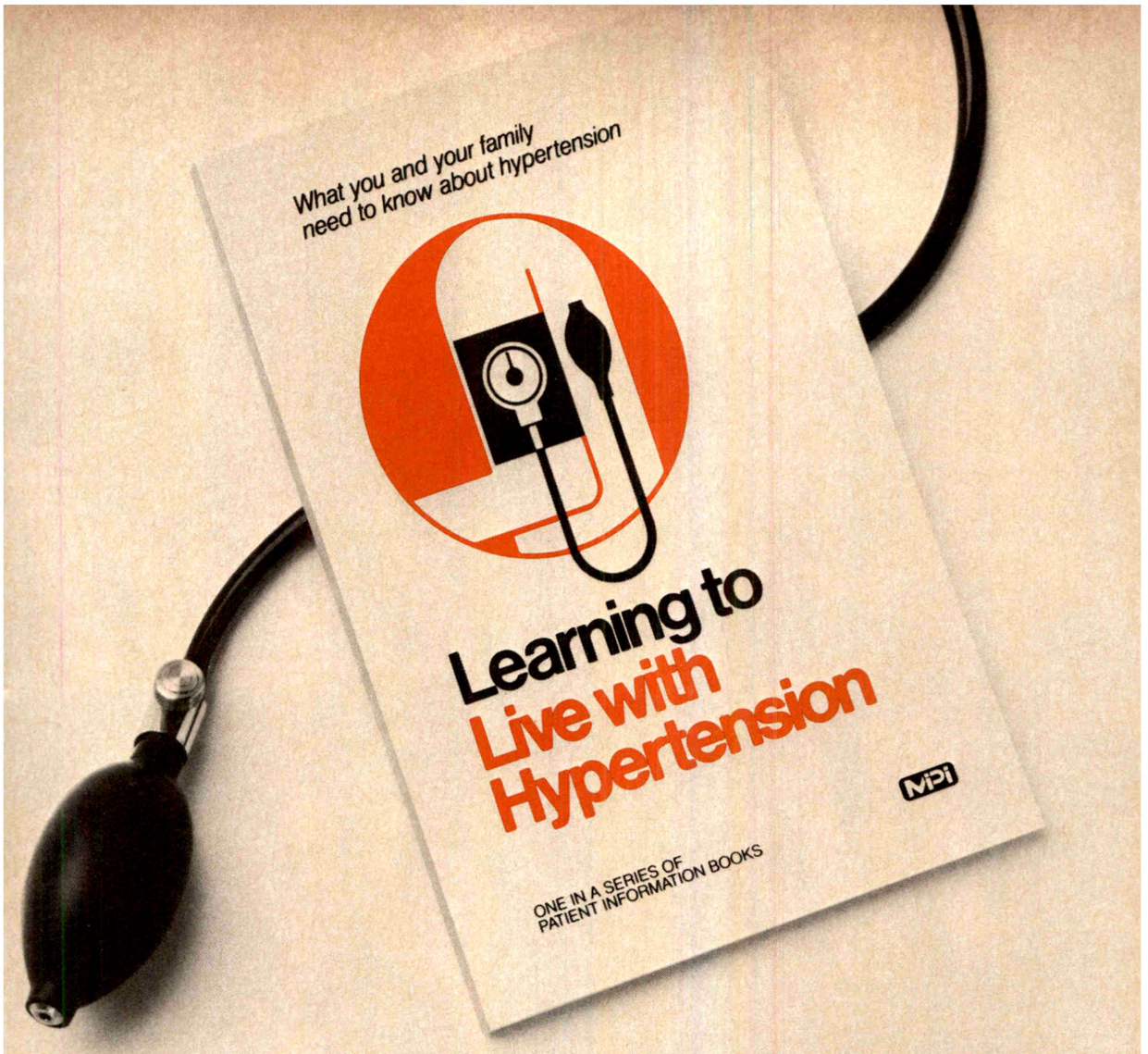

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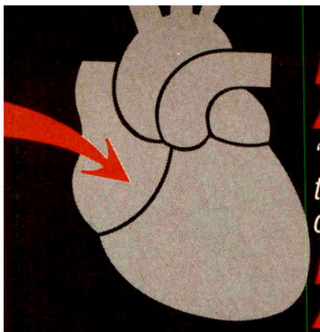

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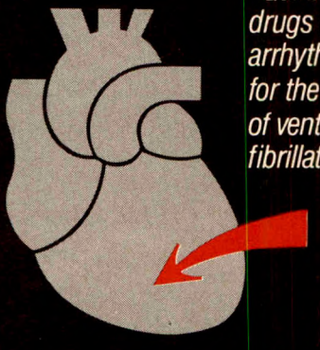

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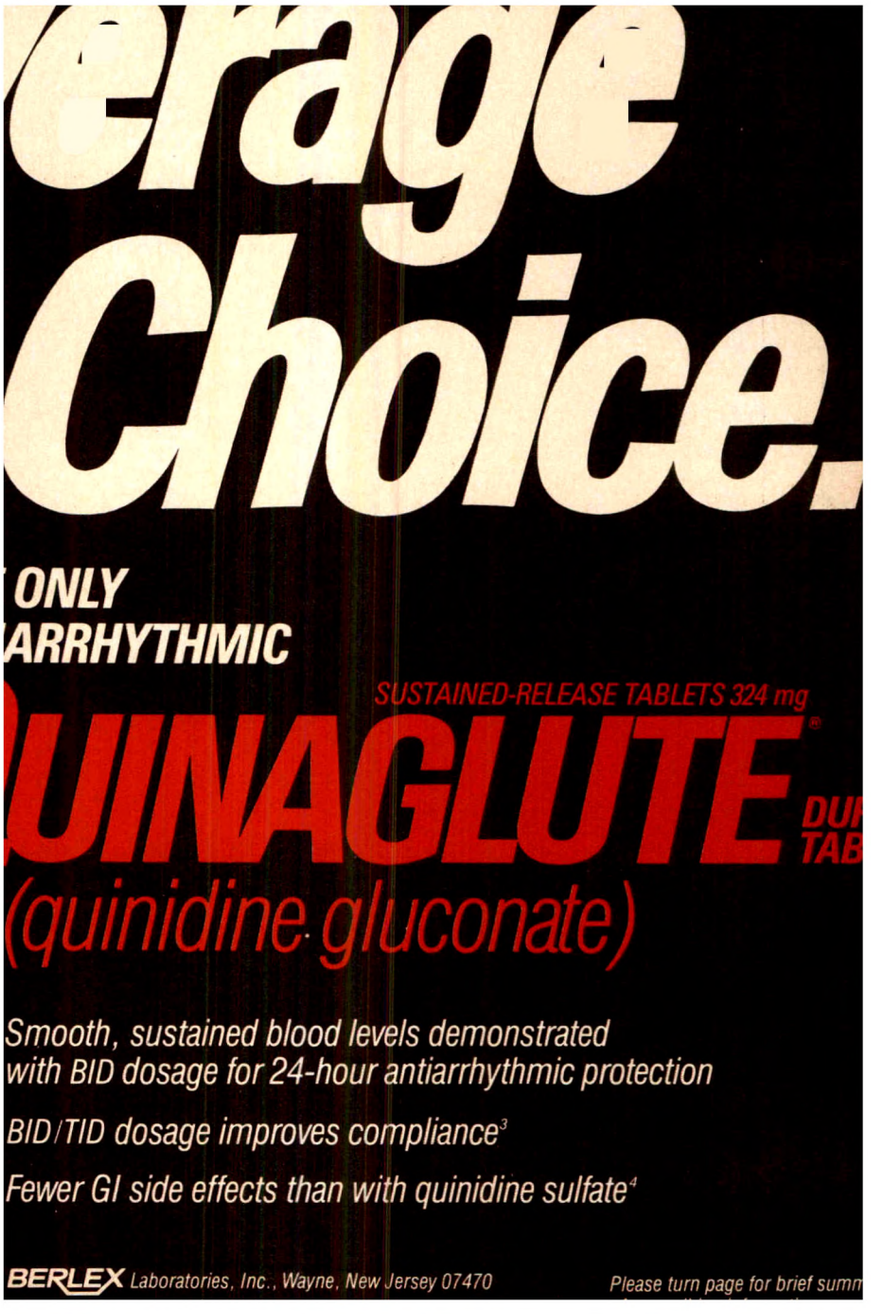
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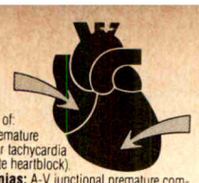

INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of: **1. Ventricular arrhythmias:** Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock). **2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.

Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.

ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea. Less frequently encountered adverse reactions:

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.

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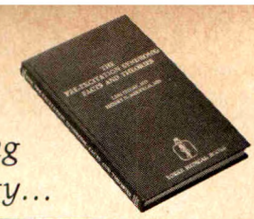

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

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- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

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The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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Association of Hyponatremia With Increased Renin Activity in Chronic Congestive Heart Failure: Impact of Diuretic Therapy

GARY L. SCHAER, MD, ANDREW B. COVIT, MD, JOHN H. LARAGH, MD, and ROBERT J. CODY, MD

A correlation between hyponatremia and increased plasma renin activity (PRA) has been reported in patients with severe congestive heart failure (CHF), implying both clinical and pathophysiologic significance. To determine the impact of diuretic therapy on this relation, we evaluated the correlation of serum sodium, prerenal azotemia (blood urea nitrogen/creatinine ratio [BUN/Cr]), and PRA in 44 patients with severe CHF who were maintained on diuretic therapy. Serum sodium level was inversely related to PRA ($r = -0.389$, $p < 0.02$). However, a significant correlation also existed between the BUN/Cr ratio and PRA ($r = 0.365$, $p < 0.025$) and an inverse correlation between serum sodium level and the BUN/Cr ratio ($r = 0.332$, $p < 0.025$). Multiple regression analysis of the 3 variables yielded significant interdependence ($p < 0.01$). To evaluate the effect of diuretic therapy, 12 patients with severe CHF discontinued diuretic therapy and received, for 1 week each, 10 and 100 mEq sodium diets in balance studies. PRA ranged from 0.14 to 16 ng/ml/h. Despite this range, there was no significant correlation between either serum sodium or BUN/Cr ratio and PRA. It is concluded that the presence of marked hyponatremia and prerenal azotemia in patients with diuretic-treated CHF may suggest increased PRA. However, substantial patient-to-patient variability limits the predictive value of these correlations. Although some clinical value may be derived from such correlations, they should not be used to draw major inferences regarding the severity of CHF or the pathophysiology of water balance in CHF.

It is a well-established observation that hyponatremia commonly occurs in patients with chronic congestive heart failure (CHF) during periods of decompensation.[1] Proposed mechanisms for this observation include increased vasopressin secretion[2,3] and decreased delivery of sodium and water to the distal diluting segment of the nephron.[4] However, another possible explanation is the use of large-dose diuretic therapy in chronic CHF when sodium intake is restricted but free water intake is not. The clinical precedent for this has been described.[5,6] Recently, a significant inverse correlation has been reported between serum sodium levels and plasma renin activity (PRA) in patients with chronic CHF.[7,8] That is, as the serum sodium level decreases, PRA increases. It has been suggested that severe hyponatremia may be a marker of increased PRA in chronic CHF.[8] However, this observation has been made in the presence of diuretic therapy or shortly after its discontinuance. The correlation of hyponatremia and increased PRA is of potential clinical and pathophysiologic importance in patients with chronic CHF. Therefore, we assessed the influence of diuretic therapy on this correlation in a cohort of patients treated with diuretics and in a cohort of patients studied in formal metabolic sodium balance after discontinuation of diuretic therapy.

From the Cardiovascular Center, Departments of Medicine and Pharmacology, New York Hospital-Cornell University Medical College, New York, New York. This study was supported in part by general CRC Grant RR-47, from the National Institutes of Health, Bethesda, Maryland. Manuscript received January 5, 1983; revised manuscript received March 1, 1983, accepted March 4, 1983.

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Methods

The study consisted of 44 patients, 37 men and 7 women aged from 20 to 79 years, with severe stable chronic CHF. Twenty-six had coronary and 18 had idiopathic etiologies of the CHF, and none had valvular disease or hypertension. The severity of the disease was manifested by functional class 3 or 4 (of 4) of the New York Heart Association classification in all patients and invasive hemodynamic studies indicating mean values for the group as follows: cardiac index, 1.70 ± 0.08 liters/min/m^2; pulmonary capillary wedge pressure, 23 ± 2 mm

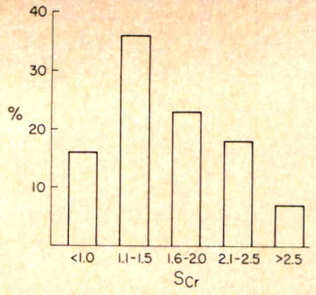

FIGURE 1. Distribution of serum creatinine levels (SCr) in the 44 patients with congestive heart failure receiving diuretics. The upper limit of normal is 1.4 mg/100 ml, and the number of patients is expressed as a percentage of total population studied.

Hg; and systemic vascular resistance, 1,958 ± 142 dynes s cm^{-5}. Exercise tolerance tests indicated marked reduction in exercise capacity in all patients. For this study, digoxin and diuretic therapy was maintained, but neither was administered in the 12 hours preceding the collection of blood samples. All patients were receiving furosemide in an average daily dosage of 97 ± 16 mg. In addition to furosemide, 13 patients were receiving a thiazide-like diuretic, 3 were receiving spironolactone, and 3 were receiving both a thiazide and spironolactone in addition to furosemide. All vasodilator drugs had been discontinued for at least 3 days before study. No overt primary glomerular disease was evident in any patient, suggesting that any renal insufficiency present was secondary to abnormalities produced by CHF. The range of serum creatinine values is shown in Figure 1.

In addition to the 44 patients receiving diuretics, 12 patients with similarly severe stable CHF (cardiac index, 2.08 ± 0.12 liters/min/m^2; pulmonary capillary wedge pressure, 23 ± 2 mm Hg; and systemic vascular resistance, 1,646 ± 71 dynes s cm^5) discontinued diuretic therapy at least 1 week. They then received 1 week each of a 10 and a 100 mEq sodium diet in balance studies. Total daily fluid intake was maintained at 2 liters and daily potassium was 60 to 80 mEq, held constant for each patient throughout the study. The only drugs maintained during this interval were digoxin in all patients and sodium warfarin when clinically indicated.

All blood samples were drawn in the morning, after overnight fast, in the supine position. Simultaneous blood samples were obtained for PRA, serum sodium, blood urea nitrogen (BUN), and serum creatinine (Cr). Plasma renin activity was estimated by radioimmunoassay of angiotensin I generated in vitro as previously reported from our laboratory,[9] and values were expressed as nanograms per milliliter per hour. In normal individuals, the normal range of PRA is based on a nomogram relating PRA to urinary sodium excretion. A normal range for this relation has not been established for patients with CHF. Serum sodium (mEq/liter), BUN (mg/dl), and serum Cr (mg/dl) were determined on a multichannel analyzer. As an index of prerenal azotemia, the BUN/Cr ratio was calculated for all patients.

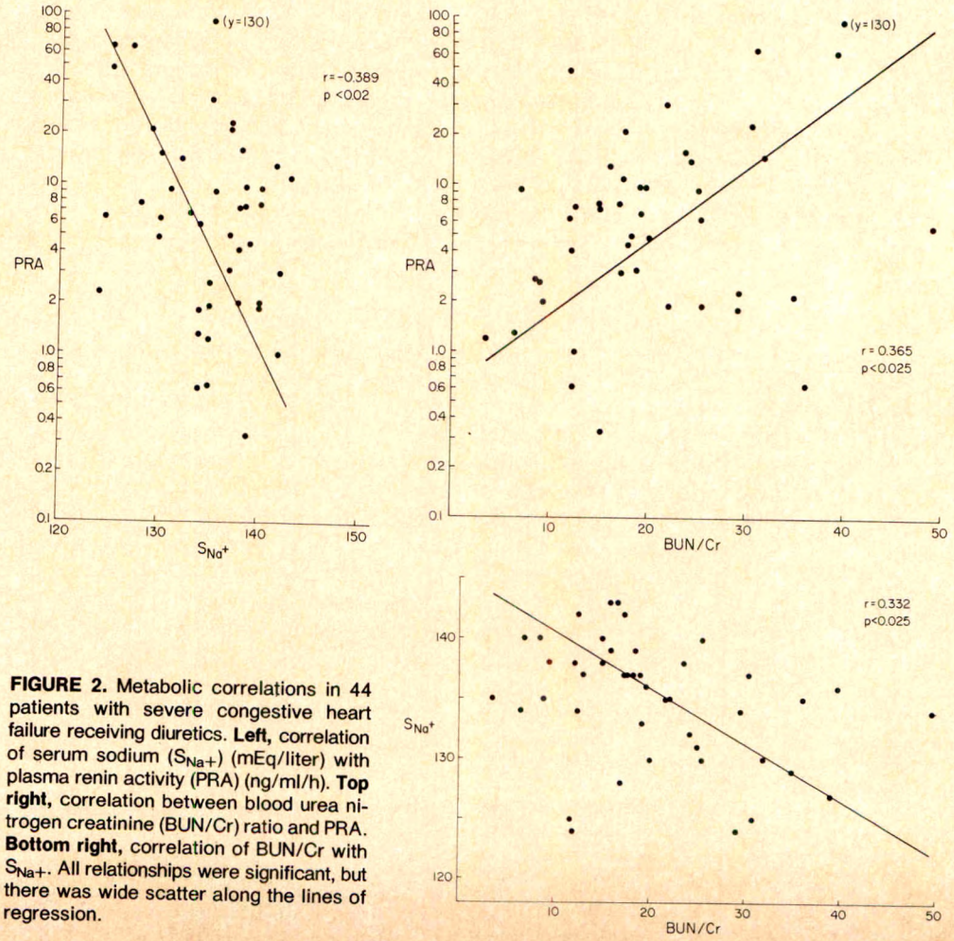

FIGURE 2. Metabolic correlations in 44 patients with severe congestive heart failure receiving diuretics. **Left,** correlation of serum sodium (S_{Na+}) (mEq/liter) with plasma renin activity (PRA) (ng/ml/h). **Top right,** correlation between blood urea nitrogen creatinine (BUN/Cr) ratio and PRA. **Bottom right,** correlation of BUN/Cr with S_{Na+}. All relationships were significant, but there was wide scatter along the lines of regression.

Linear regression analysis was used to determine the statistical significance of all correlations. As PRA is an exponential value, log transformation of this value was performed for the correlations. To assess the interrelation of PRA, serum sodium, and the BUN/Cr ratio in the 44 patients receiving diuretics, multiple linear regression analysis was used.

Results

The interrelation of serum sodium and PRA is shown in Figure 2, left. PRA ranged from 0.33 to 130 ng/ml/h. Serum sodium ranged from 124 to 146 mEq/liter. The correlation of these values was −0.389 ($p < 0.02$). However, there was wide scatter of values along the regression line, so that the index of determination was only 0.151. As prerenal azotemia is a reflection of decreased renal blood flow, a known stimulus for renin release, we then correlated the BUN/Cr ratio with baseline PRA (Fig. 2, top right). Despite similar wide scatter, the r value was 0.365, yielding statistical significance ($p < 0.025$). However, it was also clear that an inverse correlation of comparable significance was present when prerenal azotemia was correlated with serum sodium (Fig. 2, bottom right). Because of the implicit interrelation between hyponatremia, PRA, and prerenal azotemia, we then performed multiple linear regression analysis of these 3 variables, which resulted in a significance of $p < 0.01$, confirming this interrelation.

Because diuretic therapy could account for this interrelationship to a significant degree, we repeated the analysis in 12 patients with CHF who were not receiving diuretic therapy. To assess a wide range of values and the influence of sodium intake, each patient was studied on both 10 and 100 mEq sodium diets, thereby yielding 24 points of analysis (Fig. 3). For the group, PRA ranged from 0.14 to 16 ng/ml/h. Despite this 2-log range of PRA, 22 of 24 determinations of serum sodium were within a normal range of 135 to 145 mEq/liter, and 20 of 24 determinations of the BUN/Cr ratio were within a normal range of 8 to 20. As a result of this data clustering, there were no significant correlations of these 3 variables in the absence of diuretic therapy.

Discussion

Both Dzau et al[7] and Levine et al[8] reported an inverse correlation between serum sodium levels and PRA. However, Skorecki and Brenner[10] recently reemphasized that the attainment of sodium balance is of major importance in evaluating the renin-angiotensin system in CHF. In contrast to previous observations, we found that the hyponatremia-renin relation may be significantly influenced by diuretic therapy. Obviously, most patients with severe CHF are being treated with diuretics at the time of evaluation. Thus, such observations are useful clinically, if hyponatremia can identify a subgroup of patients with CHF with high PRA, as such patients are more likely to respond to converting enzyme inhibition.[11] In terms of pathophysiologic

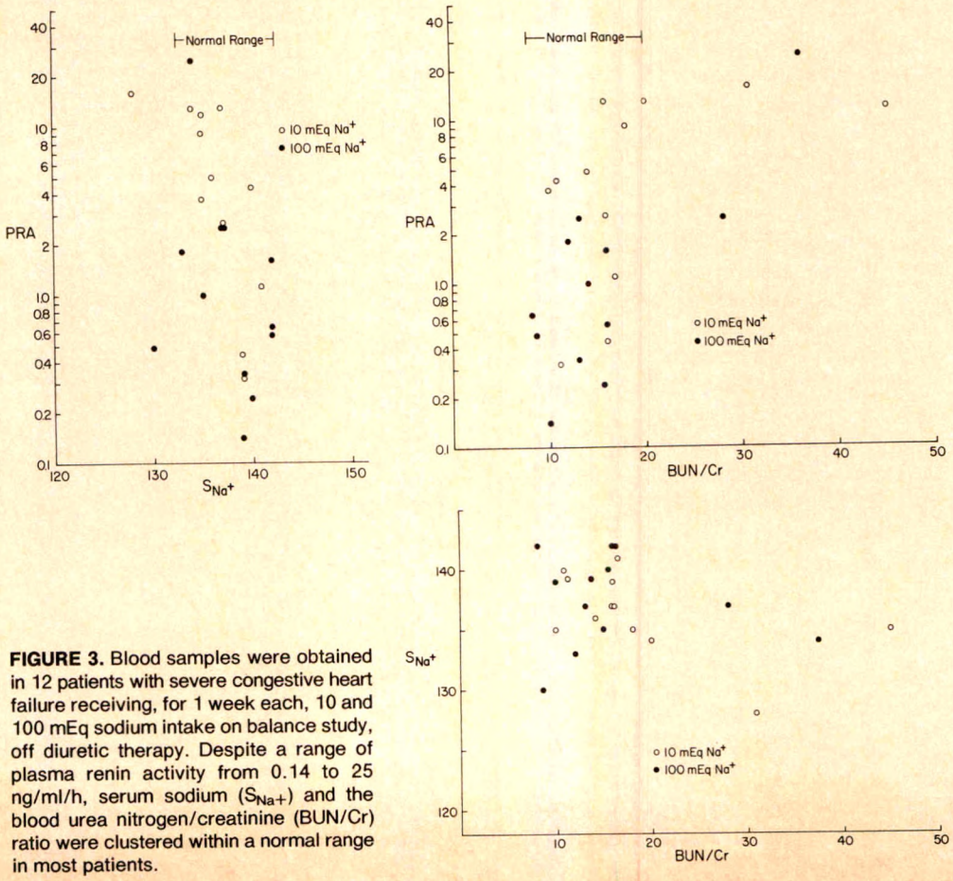

FIGURE 3. Blood samples were obtained in 12 patients with severe congestive heart failure receiving, for 1 week each, 10 and 100 mEq sodium intake on balance study, off diuretic therapy. Despite a range of plasma renin activity from 0.14 to 25 ng/ml/h, serum sodium (S_{Na+}) and the blood urea nitrogen/creatinine (BUN/Cr) ratio were clustered within a normal range in most patients.

mechanisms, the correlation of hyponatremia and increased PRA could be a manifestation of a previously reported direct angiotensin II-hypothalamic-vasopressin relation.[12]

However, classification of patients based on serum sodium[7,13] or inferences regarding vasopressin mediation of this hyponatremia,[2,8] in the setting of diuretic therapy may be an oversimplification. It is well documented that diuretic therapy, especially with the potent loop agents, can cause marked hyponatremia and prerenal azotemia,[14,15] and their hyponatremic stimulus will be even more accentuated when free water intake is not limited.[5] In CHF, diuretic therapy[16] and, for that matter, rigid sodium restriction[17] are capable of stimulating the renin-angiotensin-aldosterone axis. Additionally, through volume-depleting effects, diuretics will stimulate vasopressin secretion directly.[18] Thus, diuretic therapy by itself appears to be in a perfect position to govern the interrelation of serum sodium, prerenal azotemia, and PRA. In fact, when diuretics were discontinued and sodium and water intake was controlled, our results showed no correlation between either serum sodium or prerenal azotemia and PRA. Preliminary studies[19,20] show a lack of correlation between hyponatremia and vasopressin in patients with CHF not taking diuretics. However, a good correlation occurs between vasopressin levels and PRA.

On the basis of the present data, we would draw several conclusions. In patients with severe stable chronic CHF receiving diuretic therapy, the presence of hyponatremia and prerenal azotemia suggests that increased PRA may be evident; however, wide patient-to-patient variation of the hyperreninemia may occur. This relation may be useful in choosing a specific vasodilator, such as a converting-enzyme inhibitor to block the renin-angiotensin system, as this class of drugs yields its greatest hemodynamic improvement in the presence of increased renin-angiotensin system activity. Other vasodilators may actually increase PRA and angiotensin-induced vasoconstriction.[21] Also, this interrelation may identify those patients with high PRA in whom diuretic therapy should be decreased before administration of converting-enzyme inhibitor to avoid excessive hypotension.[22] However, in terms of pathophysiologic mechanisms hyponatremia during diuretic therapy should not be used as a marker of hormonal activity or disease severity in CHF.

Acknowledgment: We gratefully acknowledge the clinical and technical assistance of Kathleen Pondolfino, RN.

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Respiratory Gas Analysis During Exercise as a Noninvasive Measure of Lactate Concentration in Chronic Congestive Heart Failure

JOHN R. WILSON, MD, NANCY FERRARO, RN, and KARL T. WEBER, MD

Measurement of blood lactate during exercise in patients with chronic congestive heart failure provides a useful index of oxygen (O_2) availability in working muscle. Bicarbonate buffering of lactate produces carbon dioxide (CO_2) in excess of that resulting from oxidative metabolism. Therefore, calculation of excess CO_2 production from measured CO_2 production and O_2 uptake may offer a noninvasive quantitative index of changes in blood lactate during exercise in these patients. To investigate this possibility, 22 patients with congestive heart failure and depressed left ventricular function were studied during progressive maximal upright bicycle exercise. Oxygen uptake, expired carbon dioxide, arterial lactate, O_2 extraction, and cardiac output were measured at each 20 W incremental work load and peak exercise. Exercise increased $\dot{V}O_2$ from 3.5 ± 0.9 ml/min/kg at rest to 13.1 ± 2.9 ml/min/kg, O_2 extraction from 49 ± 9% at rest to 78 ± 6%, lactate from 12 ± 5 mg/dl at rest to 41 ± 15 mg/dl, and cardiac index from 1.7 ± 0.4 at rest to 3.8 ± 1.2 liters/min/m^2. The increase in lactate at each work load was linearly related to excess CO_2 production ($r = 0.92$, $p < 0.01$). Exercise was repeated the following day in 10 patients; measurements of excess CO_2 production was highly reproducible ($r = 0.98$, $p < 0.01$). Excess CO_2 production also correlated with the decrease in bicarbonate produced by exercise ($r = 0.81$), supporting the hypothesis that excess CO_2 is produced by bicarbonate buffering of lactate. Thus, calculation of excess carbon dioxide production from noninvasive measurement of respiratory gas exchange provides a reliable and reproducible method of continuously assessing alterations in lactate throughout bicycle exercise in patients with chronic congestive heart failure.

Patients with chronic congestive heart failure have a reduced aerobic exercise capacity[1–3] due to inadequate oxygen (O_2) transport to working skeletal muscle.[3–7] This impairment in O_2 transport causes working muscle to become anaerobic and to produce lactate,[3–7] with the onset and degree of lactate production being proportional to the degree of muscle underperfusion.[3,8,9] Therefore, measurement of lactate during exercise in patients with congestive heart failure provides a simple method of assessing skeletal muscle O_2 availability[5,10–13] and of grading the severity of chronic congestive heart failure.[3] Measurements of lactate for these purposes has not become widely used, however, due to the inconvenience of obtaining and assaying blood lactate levels.

Lactate released during exercise is buffered by bicarbonate, producing carbon dioxide (CO_2) in excess of that resulting from oxidative metabolism.[14–16] Theoretically, this excess CO_2 is equivalent to the difference between total expired CO_2 ($\dot{V}CO_2$) and the amount of CO_2 produced by aerobic metabolic processes.[14] Aerobic CO_2 production can be estimated by multiplying the O_2 uptake ($\dot{V}O_2$) by an estimated metabolic respiratory quotient such as 0.75.[14] Combining these 2 equations, excess CO_2 production can be estimated as $\dot{V}CO_2 - (0.75 \times \dot{V}O_2)$. This value can be calculated on a minute-by-minute basis. Therefore, this approach potentially offers a noninvasive method of describing lactate concentrations throughout exercise in patients with heart failure.

Accordingly, the present study was undertaken to determine whether the calculation of excess CO_2 production during progressive upright bicycle exercise is a reliable and reproducible measure of lactate concentration during exercise in patients with congestive heart failure. An additional objective of this study was to determine whether respiratory gas analysis, previously utilized by us to evaluate the onset of anaerobic metabolism during treadmill exercise in patients with congestive heart failure,[3] can also be utilized to assess anaerobic activity during bicycle exercise.

Methods

Patients: Twenty-two patients with chronic left ventricular dysfunction (mean ejection fraction 26 ± 10%, range 11 to 40) were studied. The mean age was 55 ± 7 years; there were 20 men and 2 women. All patients were limited by dyspnea, fa-

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TABLE I Hemodynamic and Metabolic Responses to Maximal Bicycle Exercise (n = 22)

	Work Time (min)	Load (W)	Heart Rate (beats/min)	Cardiac Index (liters/min/m^2)	PWP (mm Hg)	Oxygen Extraction (%)	Arteriovenous (ml/dl^2)	Lactate (mg/dl)
Rest	...	...	88 ± 12	1.7 ± 0.4	20 ± 10	49 ± 9	8.52 ± 1.92	12 ± 5
Exercise	6.8 ± 2.4	51 ± 18	130 ± 17†	3.8 ± 1.2*	35 ± 12†	78 ± 6†	13.63 ± 2.56†	41 ± 15*

* $p < 0.01$ compared with rest.
PWP = pulmonary wedge pressure.

TABLE II Respiratory and Blood Gas Responses to Maximal Bicycle Exercise (n = 22)

	$\dot{V}O_2$ (ml/kg/min)	R	Excess CO_2 (ml/min)	Excess CO_2 (R = 0.75) (ml/min)	pO_2 (mm Hg)	pCO_2 (mm Hg)	pH	HCO_3 (mEq/liter)
Rest	3.5 ± 0.9	0.79 ± 0.08	...	...	99 ± 13	32 ± 5	7.48 ± 0.03	23.5 ± 3.0
Exercise	13.1 ± 2.9*	1.10 ± 0.13†	303 ± 155*	336 ± 176*	108 ± 19*	27 ± 4*	7.47 ± 0.06	19.8 ± 1.8*

* $p < 0.01$ compared with rest.
R = respiratory gas exchange ratio.

tigue, or both during exercise despite administration of digoxin and diuretics and had no peripheral edema or ascites at the time of study. All patients had a decrease in peak $\dot{V}O_2$ (mean 13.1 ± 2.9 ml/min/kg) below the expected normal response (≥25 ml/min/kg).[17,18] Left ventricular dysfunction was attributed to coronary heart disease in 9 patients and to idiopathic dilated cardiomyopathy in 13.

Protocol: On the day before study, a trial maximal exercise test was performed. Exercise was performed on an upright bicycle ergometer (Monarch) and begun at a work load of 20 W. Every 3 minutes, the work load was increased by 20 W to symptomatic maximum. All exercise tests were performed at least 4 hours after meals.

The following morning, a Swan-Ganz catheter and radial arterial catheter were inserted. Thirty minutes later, maximal exercise testing was performed. Respiratory gases were measured for 5 to 10 minutes with patients at upright rest and throughout exercise. Pulmonary artery and wedge pressure recordings and pulmonary artery and arterial blood samples for O_2 saturation and lactate concentration were obtained at rest, 2 to 3 minutes into each stage of exercise, and at maximal exercise. Arterial blood samples for pH, partial pressure of carbon dioxide (pCO_2), and partial pressure of oxygen (pO_2) were also obtained at rest and at maximal exercise in 11 patients. Maximal exercise testing with respiratory gas analysis was repeated the following day in 10 patients to evaluate their reproducibility.

Measured variables: Minute oxygen consumption ($\dot{V}O_2$; milliliters per minute), minute carbon dioxide production ($\dot{V}CO_2$; milliliters per minute), and minute ventilation ($\dot{V}_E$; liters per minute) were measured with a Beckman Metabolic Cart equipped with O_2 and CO_2 analyzers (OM-11 and LB-2, respectively) and a turbine volume transducer. The respiratory gas exchange ratio was calculated as $\dot{V}CO_2/\dot{V}O_2$. Excess CO_2 was calculated every 30 seconds as ($\dot{V}CO_2 - 0.75 \cdot \dot{V}O_2$), using the $\dot{V}CO_2$ and $\dot{V}O_2$ measured during the previous 30 seconds. The metabolic respiratory quotient was arbitrarily chosen to be 0.75 as suggested by Issekutz and Rohdahl.[14] In addition, excess CO_2 was calculated using the measured resting respiratory gas exchange ratio, an estimate of the actual metabolic respiratory quotient, instead of 0.75. Excess CO_2 was expressed as milliliters produced per minute.

Arterial blood samples for lactate determination were deproteinized with cold perchloric acid and assayed with a spectrophotometric technique (normal 3 to 12 mg/dl).[19] Hemoglobin concentration was measured by Coulter Counter. Hemoglobin O_2 saturation was measured with a co-oximeter (Instrumentation Laboratories) precalibrated with human blood. Blood O_2 content was calculated as the product of hemoglobin, 1.34 ml O_2/g hemoglobin, and percent O_2 saturation. O_2 extraction was calculated as the ratio of the arteriovenous O_2 difference and arterial O_2 content. Cardiac output was calculated from the Fick principle as $\dot{V}O_2$/arteriovenous O_2 difference. Arterial blood gas samples were analyzed by a blood gas analyzer (Corning 168); bicarbonate concentration was calculated from pH and pCO_2 using a nomogram.

Statistical methods: All values are expressed as mean ± standard deviation. Linear regression analysis was performed using the method of least squares. A probability of <0.05 was considered significant.

Results

Results are summarized in Tables I and II and Figures 1 to 3. The resting cardiac index of the patients was 1.7 ± 0.4 liters/min/m^2 and the resting pulmonary wedge pressure was 20 ± 10 mm Hg.

Exercise hemodynamic findings: On the average, patients exercised for 6.8 ± 2.4 minutes (range 3 to 13) to a peak work load of 51 ± 18 W (range 20 to 100). At peak exercise, $\dot{V}O_2$ had increased from 3.5 ± 0.9 ml/min/kg at rest to 13.1 ± 2.9 ml/min/kg, while heart rate increased from resting levels of 88 ± 12 to 130 ± 17 beats/min. Cardiac index increased modestly from 1.7 ± 0.4 liters/min/m^2 at rest to 3.8 ± 1.2 liters/min/m^2; the pulmonary wedge pressure increased from resting values of 20 ± 10 to 35 ± 12 mm Hg.

Metabolic responses and respiratory gas analysis: Percent O_2 extraction was 49 ± 9% at rest and increased to 78 ± 6% at peak exercise with all but 1 patient exceeding 70% extraction. Arterial lactate concentration increased from 12 ± 5 to 41 ± 15 mg/100 ml ($p < 0.001$), the mean increase being 30 ± 15 mg/100 ml with all patients exhibiting increases >10 mg/100 ml.

Exercise resulted in a peak excess CO_2 production rate of 336 ± 176 ml/min when calculated using an assumed metabolic respiratory quotient of 0.75 and of 303 ± 155 ml/min when calculated using the measured resting respiratory gas exchange ratio of 0.79 ± 0.80.

Exercise increased the respiratory gas exchange ratio from 0.79 ± 0.80 at rest to 1.10 ± 0.13.

Dynamic changes in arterial lactate concentration and respiratory gas exchange are illustrated for 2 different patients in Figure 1. Up to 20 to 40% of peak $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ increased in proportion to $\dot{V}O_2$ while the respiratory gas exchange ratio remained stable; there was no excess CO_2 produced, and lactate did not increase. Subsequently, at ≥50% of the peak $\dot{V}O_2$, there was a progressive increase in the respiratory gas exchange ratio, excess CO_2, and lactate.

The increase in arterial lactate concentration measured at the end of each stage of exercise was linearly related to the production rate of excess CO_2 calculated from the respiratory gases obtained during the same time period. This was the case both when the excess CO_2

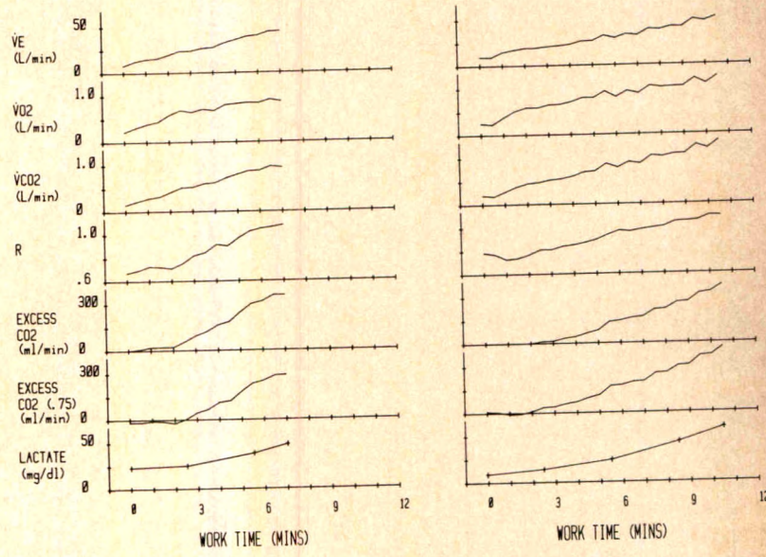

FIGURE 1. Respiratory gas exchange variables during an incremental bicycle exercise test in 2 patients with heart failure. Changes in arterial lactate paralleled changes in excess CO_2 and the respiratory gas exchange ratio (R). Excess CO_2 was calculated using the measured R and an assumed metabolic respiratory quotient of 0.75 (excess CO_2 [0.75]). Respiratory gas measurements were calculated every 30 seconds and the points connected.

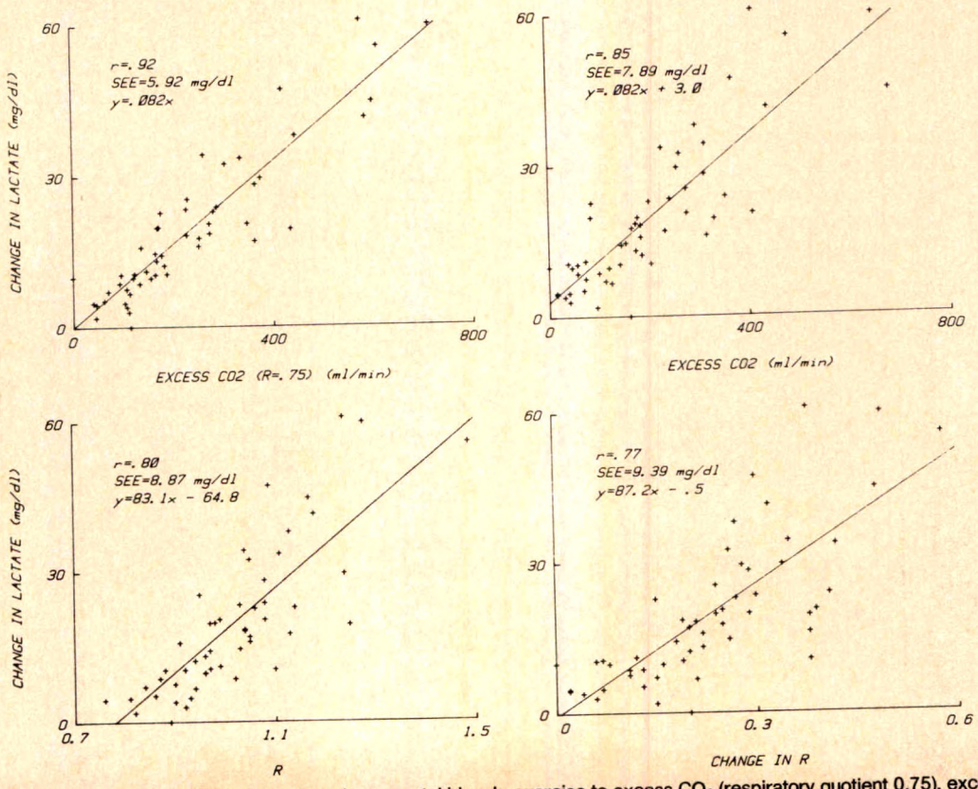

FIGURE 2. Relation of changes in arterial lactate during incremental bicycle exercise to excess CO_2 (respiratory quotient 0.75), excess CO_2 calculated using the measured resting R, R, and changes in R. Measurements were made at the end of each work load and at peak exercise in 22 patients with heart failure.

production rate was calculated using a metabolic respiratory quotient of 0.75 ($r = 0.92$, $p < 0.01$, $n = 54$) (Fig. 2) and when it was calculated using the resting respiratory gas exchange ratio as an estimate of the metabolic quotient ($r = 0.85$, $p < 0.01$, $n = 54$) (Fig. 2).

These relationships were not affected by the resting lactate concentration. In 5 of the patients, lactate levels ≥12 mg/dl were observed at rest. Excess CO_2 correlated closely with changes in lactate in all 5 of these patients. The elevated resting lactate levels were not associated with markedly impaired exercise capacity and therefore may have been due to hyperventilation during or after instrumentations; respiratory alkalosis is known to increase arterial lactate concentrations.[20,21]

The increase in lactate concentration during exercise correlated less well with the respiratory gas exchange ratio ($r = 0.80$, $p < 0.01$, $n = 54$) and with the change in this ratio ($r = 0.77$, $p < 0.01$, $n = 54$) (Fig. 2). This is to be expected since the effect which a given level of anaerobic CO_2 production has on the respiratory gas exchange ratio depends on the corresponding $\dot{V}O_2$.

Relation between bicarbonate and respiratory variables: The effect of maximal exercise on arterial blood gases and calculated bicarbonate is shown in Table II. Maximal exercise had no effect on pH (rest 7.48 ± 0.03 versus exercise 7.47 ± 0.06), but reduced the arterial pCO_2 (rest 32 ± 5 mm Hg versus exercise 27 ± 4 mm Hg; $p < 0.01$) and bicarbonate (rest 23.5 ± 3.0 mEq/liter versus exercise 19.8 ± 1.8 mEq/liter; $p < 0.01$).

At maximal exercise, the decrease in bicarbonate correlated with the minute production rate of excess CO_2 calculated using a metabolic respiratory quotient of 0.75 ($n = 11$, $r = 0.81$, $p < 0.01$) (Fig. 3) and with the minute production rate of excess CO_2 calculated using the measured resting respiratory gas exchange ratio ($r = 0.72$, $p < 0.01$).

Reproducibility: Respiratory gas measurements during maximal exercise were repeated in 10 patients. Temporal changes in ventilatory parameters were comparable to those noted during the first exercise test. The peak exercise $\dot{V}O_2$ varied by only 5 ± 6%, whereas the maximal exercise duration varied by 13 ± 8%. There was a close correlation between the excess CO_2 calculated using a metabolic respiratory quotient of 0.75 measured during test 1 and test 2 when these 2 measurements were compared at the end of identical work loads ($r = 0.98$, $p < 0.01$, $n = 21$). There was also a close relationship between respiratory gas exchange ratios measured at identical work loads ($r = 0.86$, $p < 0.01$, $n = 21$). Duplicate measurements of excess CO_2 calculated using the measured resting gas exchange ratio correlated less well ($r = 0.76$, $p < 0.01$, $n = 21$), primarily due to variations in the resting exchange ratio.

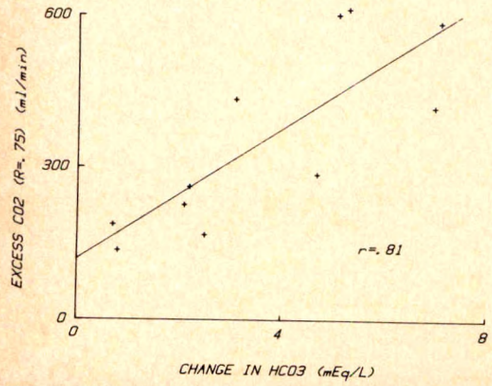

FIGURE 3. Relation of total changes in arterial bicarbonate concentration during incremental bicycle exercise to peak excess CO_2 (respiratory quotient = 0.75) in 11 patients with heart failure.

Discussion

Recently, it has been demonstrated that respiratory gas analysis can be used to identify noninvasively the onset of lactate production or the anaerobic threshold during treadmill exercise in patients with chronic heart failure.[3] This approach involves detection of the point at which a disproportionate rise in $\dot{V}CO_2$ occurs relative to $\dot{V}O_2$ and therefore is based on detecting the onset of bicarbonate-buffering of lactate and release of excess CO_2.[3,14,15] This technique does not, however, describe the rate of increase in lactate during exercise, a parameter which may correlate with the extent and severity of anaerobic activity. Moreover, the anaerobic threshold is identified by noting relatively subtle changes in respiratory gas exchange that may be difficult to identify precisely. A more complete and reliable description of anaerobic metabolic activity throughout exercise would therefore be desirable.

Respiratory gas analysis of arterial lactate: The results of the present study suggest that calculation of the rate of excess CO_2 production at any given point during exercise correlates closely and reproducibly with the total increase in arterial lactate which has occurred. This approach therefore provides a noninvasive method of continuously assessing alterations in lactate throughout exercise. The best correlation was noted when excess CO_2 was calculated based on an assumed metabolic respiratory quotient of 0.75. Calculation of excess CO_2 using this approach was also found to be most reproducible. The excess CO_2 calculated using the measured basal respiratory gas exchange ratio correlated somewhat less closely with changes in lactate and was less reproducible. This lower correlation and reproducibility was primarily due to hyperventilation-induced elevations in the basal respiratory gas exchange ratio in several patients, either at the initial study or when restudied. Thus, a major advantage of using an assumed metabolic respiratory quotient is that the presence of resting hyperventilation does not influence the calculation of excess CO_2 during exercise.

These findings are consistent with prior studies in normal subjects and patients with mitral stenosis. In 26 untrained normal subjects, Issekutz and Rohdahl[14] observed a close correlation ($r = 0.92$, $n = 102$) between changes in lactate during exercise and the minute production of excess CO_2 calculated using a respiratory quotient of 0.75. Naimark et al[15] reported similar results in 19 normal subjects and in 10 patients with mitral stenosis or primary pulmonary hypertension. Using a

breath-by-breath technique to measure the respiratory gas exchange ratio, they reported that changes in this ratio and in excess CO_2 parallel changes in lactate and bicarbonate.

Mechanism of excess CO_2 production: The close relationship noted between excess CO_2 and changes in both lactate and bicarbonate suggest that the excess CO_2 was primarily produced by bicarbonate buffering of lactic acid. However, several other factors may also have influenced CO_2 production to a lesser extent. Hyperventilation can produce a decrease in arterial pCO_2 and consequent transient release of stored CO_2. The arterial pCO_2 dropped slightly during exercise in our patients, suggesting that hyperventilation was present. However, the decrease in pCO_2 was relatively small and similar to the response noted in normal subjects during exercise.[22] Exercise-induced changes in substrate utilization by aerobic metabolic pathways could also alter excess CO_2 production. However, major changes in substrate utilization do not appear to occur during exercise.[14,15] Increases in blood temperature during exercise[23] could release small amounts of CO_2 due to the effect of temperature on blood pH. Finally, it has been suggested that marked increases in mixed venous pCO_2 during exercise may cause some release on CO_2 from storage sites.[24]

Potential limitation: This study examined the relationship between the rate of excess CO_2 production and changes in arterial lactate concentration during progressive bicycle exercise. Whether the same relationship is present using a different bicycle exercise protocol, another form of exercise, or after a major therapeutic intervention remains to be determined. In addition, the initial 20 W work load used in our protocol may cause immediate lactate production in patients with severe functional impairment. In such patients, identification of the anaerobic threshold is therefore not possible using our protocol, although characterization of the rate of lactate release still is possible using calculation of excess CO_2. In such patients, use of an exercise protocol which involves a more gradual increase in work load may be desirable.

Clinical implications: This study suggests that measurement of excess CO_2 using a metabolic respiratory quotient of 0.75 provides a reliable and reproducible index of changes in arterial lactate concentration during bicycle exercise in patients with chronic congestive heart failure. This method therefore can be used to examine the rate of lactate accumulation during exercise as well as the onset of anaerobic metabolic activity. A more complete description of anaerobic metabolism during exercise than simply identifying the onset of the anaerobic threshold is thereby provided.

This characterization of anaerobic metabolic activity during exercise can be used to grade the severity of chronic heart failure. With increasingly impaired cardiovascular function during exercise, $\dot{V}O_2$ maximal is reduced and anaerobic metabolism therefore commences earlier in exercise and at a lower level of $\dot{V}O_2$.[3,16] Documentation of the pattern of anaerobic metabolic activity during exercise therefore helps to confirm that $\dot{V}O_2$ maximal is reduced. Moreover, demonstration of an accelerated pattern of lactate accumulation during exercise can be used to identify impaired O_2 transport to working muscle in patients who are unwilling or unable to achieve their maximal $\dot{V}O_2$.

In addition, this method may be useful in evaluating the effects of therapeutic regimens on O_2 delivery to exercising muscle. Inadequate O_2 availability to working muscle increases blood lactate concentration.[3,5–7] Consequently, improved skeletal muscle O_2 availability should be associated with a delayed anaerobic threshold, a lower rate of lactate accumulation, or both after attainment of the anaerobic threshold. These changes should in turn be detectable as a reduction in excess CO_2 for any given work load.

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Conduction Disturbances Related to the Site and Severity of Mitral Anular Calcification: A 2-Dimensional Echocardiographic and Electrocardiographic Correlative Study

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To investigate an apparent association of mitral anular calcium (MAC) and electrocardiographic abnormalities, the relation between location of 2-dimensional (2-D) echo-quantified MAC and conduction disturbances was studied in 140 patients with MAC (MAC group) and in 135 age- and sex-matched patients without MAC (control group). The MAC group was subclassified regarding site and severity of calcium in the mitral anulus. The site of MAC was defined as Type I, near the primary conduction system—MAC located in the medial segment and/or extending to the anterior mitral leaflet; and Type II—MAC located at the central and/or lateral segments away from the primary conduction system. The severity of MAC was graded on 2-D echocardiography as mild (localized within 1 segment) and moderate to severe (>1 segment).

Seven patients with MAC, and only 1 control subject, had pacemakers in place. Conduction disturbances were present in 44 (31%) of 140 patients with MAC, and in 37 (27%) of 135 control patients (difference not significant). But there were more conduction disturbances in patients with Type I MAC (53%) than in those with Type II MAC (26%) ($p < 0.01$). Specifically, complete left bundle branch block and intraventricular conduction delay were more prevalent when MAC was near the conduction system. Conduction disturbances also were more prevalent in patients with Type I MAC than in the control group: intraventricular conduction delay (Type I, 12% versus control, 4%; $p < 0.05$) and total conduction disturbances (53 versus 28%; $p < 0.01$). These data suggest that moderate to severe degrees of MAC located near the conduction system are associated with conduction disturbances, especially intraventricular conduction delay.

Mitral anular calcium (MAC) or fibrosis is considered a consequence of aging and has long been associated with conduction disturbances in elderly people. Since the early 20th century, the relation between MAC and conduction disturbances has been reported in autopsy studies.[1,2] Several articles[3–7] have demonstrated the use of echocardiography in the diagnosis of MAC, underlying tissue degeneration, fibrosis, and calcium in the area of the conduction system. Most of these studies were performed with only M-mode echocardiographic analysis or with small numbers of patients, or both. The goal of this investigation was (1) comparison of the occurrence of conduction disturbances in patients with and without MAC, and (2) observation of the echocardiographic site and severity of MAC relative to associated conduction disturbances.

Although the sensitivity and specificity of echo-quantified MAC have not been well established, there is evidence that echocardiography is a sensitive tool for the detection of MAC in comparison with chest roentgenography and fluoroscopy.[3–8]

Methods

Patient selection: One hundred-forty patients with MAC and 135 age- and sex-matched subjects without MAC (control group) were studied. The patients with MAC were identified from the echocardiographic records in the Computerized Patient Data Bank of our Cardiology Division indexed between January 1980 and May 1982. Age- and sex-matched control patients with suspected cardiac disease but no evidence of echocardiographic MAC were similarly selected. We excluded patients with recent myocardial infarction, a prosthetic mitral valve, and those with a technically limited study. Conduction disturbance in the setting of infarction is a special

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consideration and patients with a prosthetic mitral valve were excluded because of the difficulties in distinguishing the dense echoes of MAC from reverberation echoes of the valve ring or stents. Recognition of associated heart disease in patients of the 2 groups was obtained from the patient data bank containing complete echocardiographic diagnostic categories based on the criteria reported previously.[9] Additionally, coronary artery disease was diagnosed if regional left ventricular wall motion abnormalities were seen by echocardiography or if there was evidence of old myocardial infarction (abnormal Q wave, coronary T wave with reciprocal ST-T change) by electrocardiography.

Echocardiographic measurements: M-mode and 2-D echocardiographic studies in the MAC group were reviewed systematically by 2 observers. Echocardiographic images were obtained with a Hewlett-Packard model 77020A, Toshiba SSH-10A, or Irex System III ultrasound imaging system utilizing a 2.25 MHz or 3.5 MHz medium focused transducer. M-mode echocardiograms were derived from the 2-D instrument and were recorded on a strip chart.

Our M-mode echocardiographic criteria for MAC are the standard criteria which have been published by others.[5–7] These criteria consist of dense echoes, more than 3 mm thick, behind the posterior mitral leaflet and anterior to the left ventricular wall endocardium, moving parallel to the left ventricular posterior wall. Two-dimensional echocardiographic criteria for MAC include (1) an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet, on long-axis view, and (2) an echo-dense structure posterior to the posterior mitral leaflet on short-axis view.

We routinely recorded 2-D echocardiographic parasternal long- and short-axis views, midprecordial long- and short-axis views, apical long-axis and 4-chamber views, and subcostal long- and short-axis views.[10] For the assessment of MAC, we particularly focused our attention on the parasternal short-axis view just above the mitral leaflet level, obtained by scanning from the aortic root toward the mitral leaflet. To record the location and extension of MAC, we prepared a diagram of the mitral anulus viewed in the short-axis view (Fig. 1). The 4 labelled segments were referenced to the posteromedial, central, and anterolateral portions of the posterior mitral anulus and the basal portion of the anterior mitral leaflet. The patients with MAC were subclassified into 2 types: Type I, near the primary conduction system (Fig. 2)—MAC located in the medial segment and/or extending to the anterior mitral leaflet; and Type II—MAC located at the central and/or lateral segments away from the primary conduction system. The degree of severity of MAC was determined both by M-mode and 2-D echocardiography. M-mode echocardiographic thickness criteria were mild (3 to 5 mm), moderate (6 to 7 mm), and severe (≥8 mm). Two-dimensional echocardiographic extent criteria were: mild (localized within 1 segment), moderate (present in 2 segments), and severe (3 or all 4 segments).

All of the 2-D echocardiographic studies had diagnostic image quality for analysis. Real-time, slow motion, and frame-by-frame analysis were carried out on an off-line video analysis system. Extended bright echoes from the calcific aortic valve and sclerotic aortic root wall may mask the presence of calcification at the basal portion of the anterior mitral leaflet. To avoid these possible errors, we carefully observed the 2-D parasternal short-axis view throughout scanning from the mitral leaflet toward the aortic valve. In the case of discordant readings regarding the location of MAC, 2-D images were reviewed and a decision was made by consensus. M-mode echocardiographic evaluation of severity of MAC was available in 130 of 140 patients, but M-mode echocardiograms were not recorded in 10 patients with limited parasternal ultrasonic window.

Electrocardiographic studies: A standard 12-lead electrocardiogram recorded within 2 weeks of the echocardiographic examination was analyzed. The clinical history and electrocardiographic indications for pacemaker placement were reviewed from the medical records of 8 patients with pacemaker implantation before echocardiography. Electrophysiologic data were not available uniformly and therefore were not included. Electrocardiographic abnormalities were categorized as arrhythmias, conduction disturbances, and other findings (sinus bradycardia, prolonged Q-T interval).

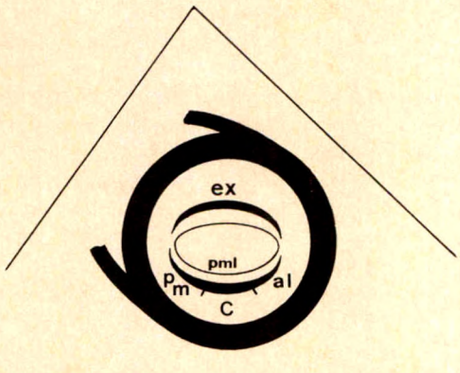

FIGURE 1. Diagram of the mitral anulus, viewed in the short-axis view, used for localization of anular calcification. The segments are referenced to the posteromedial (pm), central (C), and anterolateral (al) portions of the posterior mitral anulus and the basal portion of the anterior mitral leaflet. pml = posterior mitral leaflet; ex = extended calcification.

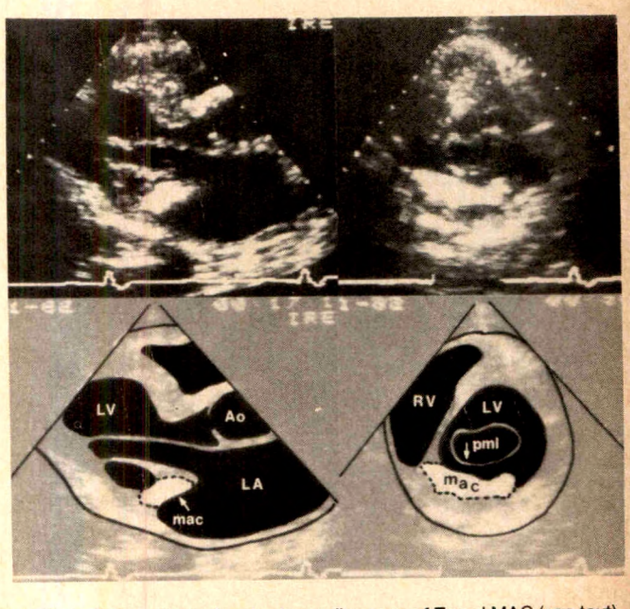

FIGURE 2. Two-dimensional echocardiograms of Type I MAC (see text). In the parasternal long-axis view (**left panels**), dense echoes representing MAC are noted (**arrow**) between the base of the posterior mitral leaflet (pml) and the posterior junction of the left atrium (LA) and left ventricle (LV). Note the medial extension of these bright echoes (MAC) toward the base of the interventricular septum on the short-axis view (**right panels**). Ao = aorta; RV = right ventricle.

TABLE I Patient Characteristics

Cardiac Condition	MAC Group (n = 140) n	%	Control Group (n = 135) n	%
Aortic stenosis or aortic stenosis with regurgitation	39	28	11	8
Coronary artery disease	17	12	30	22
Dilated cardiomyopathy	15	11	17	13
Rheumatic mitral valve disease	8	6	8	6
Aortic regurgitation	4	3	14	10
Hypertrophic cardiomyopathy	3	2	0	0
Mitral valve prolapse	2	1	8	6
Congenital heart disease	1	1	0	0
Total	89	64	88	65

Arrhythmias included atrial fibrillation, atrial flutter, and atrial or ventricular tachyarrhythmias. Conduction disturbances included atrioventricular block, right or left bundle branch block, and intraventricular conduction delay. Fascicular block was categorized by the criteria proposed by Rosenbaum et al.[11] Intraventricular conduction delay was diagnosed in the presence of a QRS duration of >120 ms when the pattern was not typical of either right or left bundle branch block. Bradycardia was defined as <50 beats/min.

Statistical analysis: Statistical analysis for the group comparison was done using the chi-square test.

Results

Patient characteristics: Ninety of the 140 patients (64%) with MAC were women and 50 patients (36%) were men. The control group consisted of 86 (64%) women and 49 men (36%). The ages of the patients with MAC ranged from 27 to 92 years (70 ± 13, mean ± standard deviation) and the ages of the patients without MAC ranged from 40 to 93 years (69 ± 11). In the MAC group, the patients had a much higher incidence of calcified aortic valve with restricted leaflet motion consistent with aortic stenosis, aortic regurgitation, or both, but had a lower incidence of coronary artery disease than the control group. Other associated heart disease was seen with similar incidence in the 2 groups (Table I).

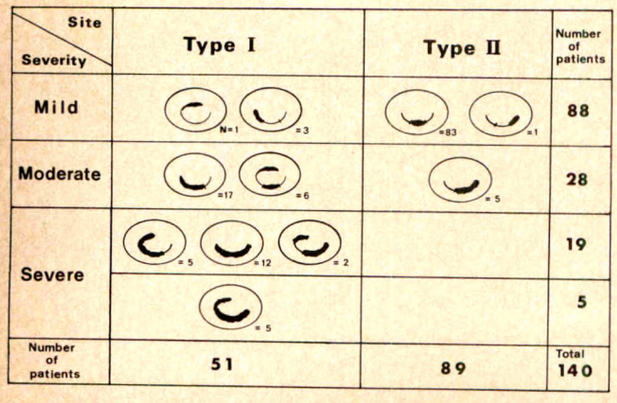

FIGURE 3. The total 140 patients with MAC were classified according to the site and severity of calcified lesions (see text for definitions).

Two-dimensional echocardiographic evaluation of MAC: There were 51 of 140 cases (36%) of Type I MAC with medial posterior location, extension to the anterior mitral leaflet, or both, and 89 of 140 (64%) of Type II MAC with central or lateral location, or both. In grading MAC for severity, we found 88 of 140 (63%) mild (located in 1 segment), 28 of 140 (20%) moderate (located in 2 segments), and 24 of 140 (17%) severe cases (3 or all 4 segments). All severe cases were medial (Type I) and most of the mild cases were in Type II (Fig. 3). Extension of calcification onto the anterior mitral leaflet was noted as a continuous set of bright echoes from the medial portion of the anulus or as a continuous dense set of echoes from the posterior aortic wall. J-shaped or U-shaped configuration of bright echoes surrounding the mitral orifice were observed in severe MAC cases.

M-mode echocardiographic evaluation of MAC: The severity of MAC by M-mode criteria was mild in 79 of 130 (61%), moderate in 41 of 130 (32%), and severe in 10 of 130 (8%). Eighty-six of 130 cases (66%) had the same grade of severity seen by M-mode and 2-D echocardiography. The remaining 44 of 130 patients (34%) fell into an unmatched group regarding grade and extent of severity (Fig. 4).

Incidence of conduction disturbances in patients with and without MAC: Conduction disturbances were found in 50 of 140 patients (36%) with MAC, and in 38 of 135 patients (28%) without MAC (Table II). Arrhythmias were found in 24% of patients with MAC and in 21% of patients without MAC. There were no statistically significant differences, either for type of conduction disturbance or arrhythmia, between the 2 groups if subgrouping was not performed. Seven patients in the MAC group had previously implanted pacemakers; however, this was true in only 1 control patient. In the MAC group, electrocardiographic findings before pacemaker implantation were sick sinus syndrome (2 cases), atrial fibrillation with intermittent heart block (1 case), second-degree atrioventricular block (1 case), and complete atrioventricular block (3 cases). Third-degree block was the reason for pacemaker placement in the 1 control patient without MAC (who had echocardiographic study for possible pericardial effusion during radiation for carcinoma of the breast). By surveying the medical records of the patients with pacemakers, we noted that 2 patients with MAC and a control patient without MAC had a documented episode of syncope related to conduction system disease. There were 6 patients in the MAC group and 2 in the control group with second- or third-degree atrioventricular block. There was no statistical difference in the incidence of heart block (second or third degree) between the 2 groups.

Incidence of conduction disturbances related to the site of MAC (Table II): Medial Type I MAC had much higher incidence (27 of 51, 53%) of conduction disturbances than Type II (23 of 89, 26%; $p < 0.01$). Specifically, complete left bundle branch block (Type I: 7 of 51, 14% versus Type II: 2 of 89, 2%; $p < 0.01$) and intraventricular conduction delay (Type I: 6 of 51, 12% versus Type II: 2 of 89, 2%, $p < 0.05$) were noted with significantly higher incidence in the Type I group. The

TABLE II Incidence of Electrocardiographic Abnormalities in Patients With and Without MAC

	MAC Group					
	Type I		Type II		Control Group	
	n	%	n	%	n	%
Total cases	51	...	89	...	135	...
Normal electrocardiographic cases	16	31	51	57	68	50
Total conduction disturbances	27	53*†	23	26‡	38	28
Left anterior hemiblock	4	8	3	3	6	4
Left posterior hemiblock	0	...	0	...	1	1
Bifascicular block	0	...	2	2	2	1
Complete right bundle branch block	2	4	3	3	5	4
Complete left bundle branch block	7	14*§	2	2‡	9	7
Intraventricular conduction delay	6	12‖¶	2	2‡	5	4
P-R interval >0.20 second						
Second-degree atrioventricular block	0	...	2	2	0	...
Third-degree atrioventricular block	2	4	2	2	2	1
Implanted pacemakers	4	8	3	3	1	1
Total arrhythmia cases	12	24	21	24	29	21
Atrial fibrillation	12	24	18	20	27	20
Atrial flutter	0	...	3	3	2	1
Atrial/ventricular tachyarrhythmias	0	...	0	...	0	...
Sinus bradycardia	2	4	1	1	2	1
Prolonged Q-T interval	1	2	1	1	4	3

* $p < 0.01$, Type I versus Type II.
† $p < 0.01$, Type I versus control group.
‡ p = not significant; Type II versus control group.
§ p = not significant; Type I versus control group.
‖ $p < 0.05$; Type I versus Type II.
¶ $p < 0.05$; Type I versus control group.

incidence of intraventricular conduction delay and all conduction disturbances also were higher in Type I MAC compared with the control group.

Relationship between the conduction disturbances and the severity of 2-dimensional quantified MAC: Conduction disturbances were found in 27 of 88 (31%) patients with mild MAC and in 23 of 52 patients (44%) with moderate to severe MAC. There were no statistically significant differences in the incidence of aggregate conduction disturbances comparing the mild and the moderate to severe MAC groups. However, both complete left bundle branch block and intraventricular conduction delay specifically were more frequently seen in moderate to severe cases compared with the mild cases (both $p < 0.05$). Only intraventricular conduction delay occurred with much higher incidence in the moderate to severe MAC group compared with the control group ($p < 0.05$).

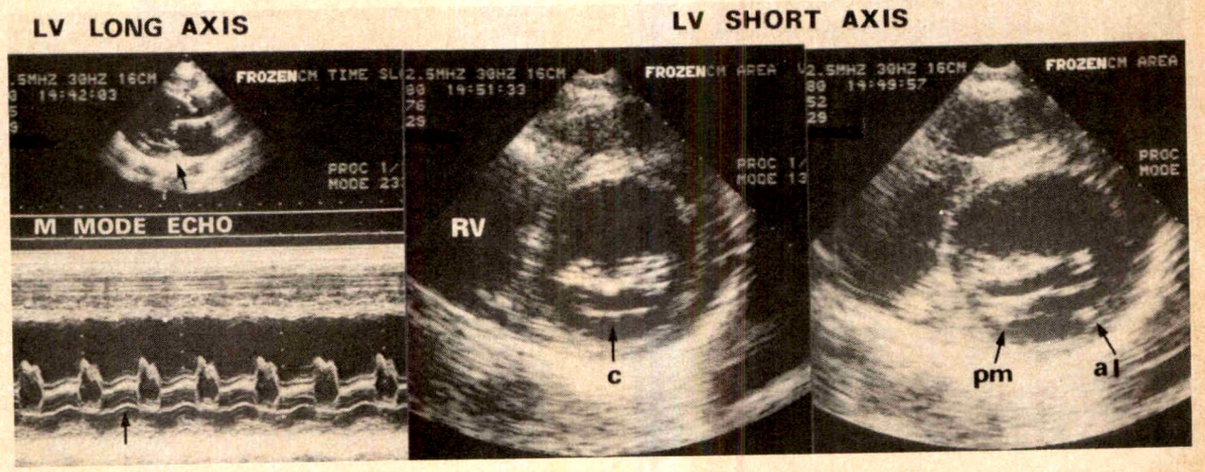

FIGURE 4. Echocardiograms labelled as mild MAC by M-mode echocardiographic criteria, but classified as severe MAC by 2-dimensional echocardiographic criteria (see text). Accurate recognition of the extent of MAC may not be available from a single short-axis view. The **center and right panels** show bright echoes from the central (c) portion of the anulus at 1 tomographic level and bright echoes from the posteromedial (pm) and anterolateral (al) portions at another level.

Discussion

MAC has been studied by pathologists for many years as a possible cause of conduction disturbances.[12–14] There is a wide spectrum of MAC, from microscopic lesions to massive calcification, but only the more severe cases of MAC can be detected by chest roentgenography or fluoroscopy.[15–16] These techniques have not been performed serially or quantitatively so the natural history of the condition is not clear. The echocardiographic features of MAC were first noted in 1973, as associated with mitral regurgitation.[17] Since then, several echocardiographic studies of MAC have been published.[3–7,18–23] There has been some discussion about the reliability of echocardiographically quantified MAC,[23,24] but we believe echocardiography has a reasonably high sensitivity of approximately 70%, judged by surgery or autopsy.[25] In addition, echocardiographic detection of MAC is increasing with the evolution of high resolution ultrasonic imaging equipment which also provides improved echo amplitude information now used to help note tissue characteristics.[26]

A relation between conduction disturbances and MAC has been reported but whether this is a causative relationship remains controversial. The previously reported incidence of conduction disturbances in patients with MAC has varied from 26 to 70%.[3–7] D'Cruz et al[3] found atrioventricular or intraventricular conduction defects in 52% of 38 patients with MAC. However, they commented that only complete right bundle branch block occurred significantly more often in their MAC group compared with control subjects without MAC (by echocardiography). Nair et al[5] reported a 70% incidence of conduction disturbances in their MAC group versus 34% in control subjects. Conversely, the same group later studied the incidence of MAC in 68 patients with symptomatic bradyarrhythmias who subsequently underwent pacemaker implantation, and reported an 87% incidence of MAC.[7] Some articles note prominence of Adams-Stokes syndrome in patients with MAC.[27,28] The occurrence of both conduction disturbances and MAC seem to increase with age and patient selection may be a factor in the figures reported in various series.

The present study showed no difference of overall incidence of conduction disturbances in the MAC group and our age-matched control group with heart disease. However, there were statistically increased incidences of intraventricular conduction delay alone and aggregate conduction disturbances in patients with medial Type I MAC and in those with moderate to severe MAC, compared with the control group. This suggests that MAC specifically involving the area adjacent to the bundle of His and its primary branches may be etiologically related to conduction disturbances. All severe cases of MAC involved this area (Type I) so advanced tissue degeneration may be the common factor in MAC and abnormal conduction. Only 4 of our 140 cases with MAC had a mild degree of calcification of the presumed critical medial area of the anulus near the septum. The site of MAC has not been assessed this way previously.

Limitations of M-mode and 2-dimensional echocardiography for the evaluation of MAC: M-mode echocardiography seems quite sensitive to the presence of MAC, but it does not discern medial extension within the mitral anulus that we suggest is associated with an increased prevalence of conduction disturbances. Thus, 2-D echocardiography is preferred to analyze MAC.[26] We evaluated the severity of MAC by the 2 methods (M-mode and 2-D echocardiographic criteria) with discrepancy of the methods in 34% of patients. This may be explained by the 2 criteria for severity of MAC being qualitatively different. In the presence of MAC, dense echo-producing structures behind the posterior mitral leaflet where echo reflections normally are not seen may be seen with either echocardiographic method. It is not difficult to note these extra echoes, that typically have an intensity equal to or exceeding that from the aortic wall or pericardium. There was no discrepancy between the 2 independent interpreters in this study. The echocardiographic criteria for MAC are based on the nonquantified increased amplitude of the echo signals, so some diagnostic difficulties may exist in differentiation of calcified lesions from fibrous or sclerotic lesions which present similar echocardiographic features. Fulkerson et al[24] commented that echocardiography was too sensitive for the detection of MAC. Our study demonstrates that echocardiographically diagnosed MAC often may include clinically insignificant findings regarding conduction disturbances.

Clinical background of the studied population: Most patients referred to our echocardiographic laboratory have heart disease of some type. Thus, we used such patients as a reasonable control group when trying to learn whether finding MAC had special significance with regard to coincidentally found conduction disturbances in a hospital laboratory. This surely accounts for the prevalence of conduction disturbances in our control group, but this is part of the answer we sought. Our study suggests the finding of MAC deserves clinical notation only if it is of moderate to severe degree and it is located near the conduction system. We currently have no data on the natural history of patients with calcium in this location.

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Analysis of Surgical Versus Medical Therapy in Active Complicated Native Valve Infective Endocarditis

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From 1972 to 1980, 23 patients (Group A) with native valve infective endocarditis underwent surgical intervention, often for multiple indications, during the active stage of the infective process because of progressive class III and IV (New York Heart Association) heart failure (12 patients), persistent severe hypotension (3 patients), uncontrolled infection for over 21 days (11 patients), aortic root abscess (2 patients), and pericarditis (1 patient). Eighty-five patients (Group B) with active native valve endocarditis, matched for severity of illness, were treated medically. Two patients (9%) in Group A and 43 patients (51%) in Group B died during the hospital admission ($p < 0.001$). Any difference in long-term cumulative survival rate between the 2 groups was largely due to the beneficial impact of surgical management on the hospital mortality. Of 23 patients in Group A, 11 (48%) had an entirely uncomplicated postoperative course. Long-term mortality rates in those with aortic valve endocarditis treated medically (79%) were significantly higher than in those with mitral valve involvement (47%) ($p < 0.05$). Patients with aortic valve involvement treated surgically had a better hospital ($p < 0.005$) and long-term ($p < 0.0005$) survival rate than those treated medically. Two groups at risk for postoperative complications were identified; 3 of 11 patients (27%) with uncontrolled infection had an early postoperative recurrence, and 4 of 7 patients (57%) with an aortic root abscess had postoperative prosthetic paravalvular regurgitation.

Surgery therefore effects a substantial reduction in hospital mortality in patients with complicated active infective endocarditis (9% versus 51%), but patients with preoperative prolonged periods of uncontrolled infection or with aortic root abscess are liable to postoperative complications.

The last 50 years have seen not only significant changes in the epidemiology of infective endocarditis,[1–4] but also major advances in its therapy. The introduction of antibiotics resulted in survival rates of 50 to 85%[1,2,4,5] in a previously almost uniformly fatal disease,[3] and replaced persistent septicemia with congestive heart failure secondary to valvular destruction[6,7] as the leading cause of death in these patients. More recently, valve replacement in the presence of active infection has been demonstrated to be of value.[8–10] A number of reports of absolute survival rates in surgical series have been published,[9,11–14] as have comparisons of surgery in active and healed infection[9,14,15] and of surgical series with unselected and unmatched medical series.[10–16] The latter comparisons[10–16] were further biased since major complications generally resulted in surgical treatment. The magnitude of the impact of surgery during active endocarditis on mortality has, therefore, not been measured in any direct comparison of surgical and medical management in well-matched patients. This report describes the findings in such an analysis of patients with active infective endocarditis. In addition, it identifies subsets of patients at risk for postoperative complications and defines the role of preoperative cardiac catheterization.

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Methods

Patients: Two hundred fifty-two patients treated for active infective endocarditis between January 1972 and March 1980 were reviewed. Of this group, 23 patients (Group A) (13 men, 10 women) underwent cardiac surgery during the active stage

TABLE I Indications for Surgery (Group A) and Criteria for Inclusion in Group B

	Group A (23 Patients)		Group B (85 Patients)		
	n	%	n	%	p Value
CHF (class III and IV, NYHA)	18	78	63	74	NS
Persistent infection	11	48	29	34	NS
Persistent systemic hypotension	3	13	10	12	NS
Root abscess	2	9	1	1	NS
Pericarditis	1	4	1	1	NS

CHF = congestive heart failure; NYHA = New York Heart Association; NS = not significant.

TABLE II Site of Involvement by Endocarditis

	Group A (23 Patients)		Group B (85 Patients)		
	n	%	n	%	p Value*
Mitral	5	22	32	38	NS
Aortic	14	61	28	33	<0.05
Mitral + aortic	4	17	19	22	NS
Mitral + aortic + tricuspid	0	...	2	2	...
Mitral + tricuspid	0	...	3	4	...
Aortic + tricuspid	0	...	1	1	...

NS = not significant; PDA = patent ductus arteriosus; VSD = ventricular septal defect.
* For group comparison, p = 0.079.

of infective endocarditis involving native heart valves. All patients were still receiving intravenous antibiotics at the time of surgery for clinically apparent ongoing bacterial endocarditis and fulfilled at least 1 of the following criteria defining persistent infection[6,8,9,15–17]: (1) positive blood cultures within 1 week before operation; (2) perianular or intramyocardial abscess at surgery; (3) clinical picture of decreasing hemoglobin level, fever, general malaise and hematuria cured by surgery; (4) a positive culture from the excised valve; (5) a positive Gram stain from the excised valve; or (6) histologic evidence of active inflammation in the excised valve.

Indications for surgery were often multiple and included at least 1 of the following: (1) moderate or severe congestive heart failure (New York Heart Association[18] class III or IV) irrespective of the type and amount of antifailure therapy; (2) active infection (positive blood cultures, typical clinical picture as defined above, or both) persisting for more than 21 days, despite adequate intravenous therapy with at least 2 well-selected bactericidal antibiotics; (3) persistent hypotension (defined as systolic blood pressure <90 mm Hg, oliguria, poor peripheral pulses, and mental confusion) due to the severity of valvular disease and requiring inotropic support; (4) new onset heart block (except first-degree heart block) suggesting a root abscess[9,19,20]; and (5) suppurative pericarditis.

An additional 85 patients (Group B) were identified during the same period. These patients were all treated conservatively with appropriate intravenous bactericidal antibiotics, therapy for congestive heart failure, and general supportive care for native valve endocarditis, but all fulfilled criteria as suggested by others,[6,8–10,16,17] and as defined above, for surgical intervention at a time when they had clinically active endocarditis. Patients in Group B did not undergo operation, primarily because of the individual physician's attitudes toward cardiac surgery during active infective endocarditis. Although surgery was, at other times, contemplated, this was postponed while further medical measures were instituted.

Other investigators have suggested that patients with left-sided Staphylococcus aureus endocarditis,[10] persistent Gram-negative endocarditis,[6,14,15] fungal endocarditis,[6,10,14,21] or recurrent emboli[10,14,15] should be operated on. Since no patient in Group A underwent surgery primarily for any of the above reasons, these criteria were not considered in selecting patients in Group B.

Surgery: Patients received mechanical prostheses during the initial part of the study. Later, because of the inconvenience of the required anticoagulant therapy, we preferentially employed the Carpentier-Edwards glutaraldehyde-preserved porcine heterograft. Postoperative antibiotic therapy, individually tailored according to organism, preoperative length of treatment, and intraoperative findings, was generally continued for 14 to 21 days.

Follow-up analysis: Patients were seen every 3 months after discharge. Mean time of follow-up was 24 months in Group A and 33 months in Group B. Full follow-up information up until the end of the study was available in 21 (91%) of 23 patients in Group A and in 74 (87%) of 85 patients in Group B.

Statistical analysis: Comparison of ages between the 2 groups was made using the Mann-Whitney U test[22] because of the skewness in the age distribution. Fisher's exact test[22] was employed in comparisons of 2 proportions. Comparisons of 2 groups on the basis of a categorical variable for which there were more than 2 categories were made using the chi-square test. Survival curves for the surgical and nonsurgical groups were constructed using the Kaplan-Meier technique,[23] and curves were compared by the modified Wilcoxon Text.[24] All p values quoted are 2-tailed.

Results

General characteristics: The age of Group A patients ranged from 10 to 54 years (29 ± 12, mean ± standard deviation) and was not significantly different from those in Group B who ranged from 13 to 85 years (35 ± 18, mean ± standard

TABLE III Infecting Organisms

	Group A (23 Patients)	Group B 85 (Patients)
Culture negative	12	40
Staphylococcus aureus	2	13
Staphylococcus epidermidis	2	3
Enterococcus	1	4
Pneumococcus	1	3
Escherichia coli	1	0
Escherichia coli + pseudomonas	1	0
Neisseria gonorrhoeae	1	0
Fusobacterium sp.	1	0
Corynebacterium sp.	1	0
Streptococcus viridans	0	8
Hemophilus parainfluenza	0	3
Hemophilus aphrophilus	0	2
Hemophilus influenza	0	1
Rickettsia sp.	0	2
Rickettsia + beta-hemolytic streptococcus	0	1
Anhemolytic streptococcus + diptheroid sp.	0	1
Coxiella burnetti	0	2
Flavobacterium sp.	0	1
Listeria monocytogenes	0	1

deviation). Likewise, there was no significant difference between the groups with regard to sex distribution or year of entry into the study.

Indications for surgery: The indications for surgery in Group A and for inclusion in Group B are listed in Table I. There was no significant difference in the frequency of these various indications between Groups A and B. While more than 1 indication was often present, the 2 main indications in both groups were congestive heart failure and persistent infection. It is noteworthy that although 2 patients underwent surgery because of clinically suspected root abscess, this was a finding in a further 5 patients at operation.

Site of involvement by endocarditis: Table II illustrates the frequency with which various valves were involved by the infective process in the 2 groups. Four patients had double valve replacements. Apart from isolated aortic valve involvement, there was no significant difference between Groups A and B in the frequencies with which the various valves were involved (for overall group comparison $p = 0.079$).

Organisms: An organism was not identified in 12 patients in Group A and in 40 patients in Group B (difference not significant) (Table III). In each patient in Group A, however, infective endocarditis was confirmed at surgery. Furthermore, postmortem examinations obtained in 31 of the 43 patients who died during the initial hospitalization in Group B confirmed endocarditis in each case. A wide variety of organisms was encountered in both groups (Table III), but individual numbers were, on the whole, too small to make adequate comparisons.

Cardiac catheterization: Nine of the 23 patients in Group A underwent preoperative cardiac catheterization. This procedure identified additional valvular regurgitation, not recognized clinically, in 4 of these 9 patients. Preoperative cardiac catheterization, however, obtained in 4 of 7 patients shown to have a root abscess at surgery failed to identify this complication in any of the 4 cases. None of the 9 patients who were catheterized died in the hospital. Two of 14 who did not undergo catheterization died in the hospital. A review of these 14, however, revealed that catheterization would not have led to any change in management in the 2 patients who died in the hospital and would have altered management in 1 of the total group of 14 patients.

Cardiac catheterization was performed in 7 of 85 patients in Group B. In none were the derived data considered to have added materially to information already available from the bedside evaluation. Two of these 7 patients survived the hospital admission. No complications occurred as a result of cardiac catheterization in this total group of 16 patients in Groups A and B.

Intraoperative and in-hospital postoperative complications: No patient died intraoperatively. The postoperative course was entirely uncomplicated in 11 patients (48%). Postoperative complications included transient hypotension (3 patients), class IV (New York Heart Association[18]) heart failure (2 patients), mediastinal hemorrhage (3 patients), and nonseptic pericarditis (2 patients).

Early postoperative recurrence: There were 3 early postoperative recurrences (defined as the reappearance of typical clinical symptoms and signs with or without confirmatory blood cultures within 8 weeks after surgery) in Group A. All 3 belonged to the group of 11 patients with uncontrolled infection for more than 21 days before surgery (27%). Of these 3 patients, 2 died of recurrent culture-negative and rickettsial endocarditis, respectively. A third patient with recurrent Staphylococcus aureus endocarditis was successfully treated with antibiotics.

Comparison of in-hospital mortality: There were 2 in-hospital deaths (9%), both due to congestive heart failure, in Group A and 43 deaths (51%) in Group B ($p < 0.001$).

Postmortem examination was performed in 31 (72%) of the 43 patients who died during the acute illness. Bacterial endocarditis was confirmed in every case. On the basis of clinical and available pathologic information, the cause of death was directly attributed to intractable congestive heart failure in 22 patients, and to congestive heart failure in combination with another factor in a further 14 patients. Meningitis, cerebral emboli, rupture of a splenic artery mycotic aneurysm, ventricular fibrillation, and renal failure were considered to be the causes of death in other patients.

Congestive heart failure alone was the indication for surgery in 9 patients in Group A and the criterion for inclusion of 41 patients in Group B. The in-hospital mortality rate in this subset of patients was 11% (1 patient) and 56% (23 patients) in Groups A and B, respectively ($p < 0.05$).

Persistent infection alone was the indication for surgery (Group A) in 3 patients and for inclusion in Group B in 5 patients. All 3 in Group A lived. One patient (20%) in Group B died (not significant). Considering all patients with persistent infection, either alone or in association with other factors, 1 of 11 died in Group A (9%) and 10 of 29 died in Group B (34%) ($p = 0.233$).

Long-term complications: Twenty-one patients in Group A were followed for a mean time of 24 months (range 3 to 102) and 42 patients in Group B were similarly followed for a mean time of 33 months (range 3 to 103).

The long-term complications in Groups A and B are listed in Table IV. Ten of 21 patients in Group A discharged from the hospital had an uneventful long-term course. Of note is that late symptomatic valvular dehiscence was noted in 5 patients (24%) in Group A. All 5 involved an aortic prosthesis. Two additional patients (9%) had asymptomatic valvular dehiscence.

Apart from coronary emboli, there were no differences in the incidences of various long-term complications between the 2 groups.

Long-term mortality rates: Cumulative survival curves for all patients in Groups A and B are plotted in Figure 1. Plots are extended until the last death in each group. The overall survival rate for patients in Group A is significantly better than that for patients in Group B at the end of the follow-up

TABLE IV Major Long-Term Complications After Discharge

	Group A (21 Patients)		Group B (42 Patients)		
	n	%	n	%	p Value
Uncomplicated	10	48	14	33	NS
Symptomatic VD	5	24	...	...	...
Asymptomatic VD	2	9	...	...	...
CHF, class IV (NYHA)	5	24	9	21	NS
Valve replacement	1	5	6	14	NS
Late recurrence	1	5	3	7	NS
Emboli					
Cerebral	2	10	0	...	NS
Mesenteric	0	...	1	2	NS
Peripheral (large vessel)	0	...	1	2	NS
Coronary	0	...	2	5	<0.05
Anticoagulant hemorrhage	0	...	1	2	NS

CHF = congestive heart failure; NS = not significant; NYHA = New York Heart Association; VD = valve dehiscence.

period (p = 0.0004). Figure 2 contrasts the survival rates of those patients in Groups A and B who survived the hospital admission. There is no significant difference in the survival rates after discharge (p = 0.624).

Poor prognostic factors in Group B and comparisons with outcome in Group A: Considering Group B only, the hospital mortality rate in medically treated patients with aortic valve involvement only (64%) was not significantly greater than in those with mitral involvement only (38%) (not significant). There was a significant difference, though, in long-term mortality rates between those with aortic (22 patients, 79%) and mitral involvement (15 patients, 47%) (p <0.05). Aortic valve involvement, therefore, carried an unfavorable long-term prognosis in moderately and severely ill patients with endocarditis treated medically. Surgically treated patients (Group A) with endocarditis of the aortic valve only had both a lower hospital (0 versus 64%, p <0.005) and long-term mortality (29 versus 79%; p <0.0005) than those treated medically (Group B).

Systemic hypotension was a particularly ominous sign in those treated medically. All 10 patients (100%) in Group B with persistent hypotension died despite hemodynamic monitoring and various combinations of vasopressor agents, digoxin, diuretics, and vasodilators. None of the 3 patients in Group A who underwent surgery for systemic hypotension died in the hospital (p <0.0005). These 3 patients have been followed for 30, 34, and 58 months, respectively.

An aortic root abscess was clinically suspected in 1 patient in Group B. He had Mobitz II second-degree atrioventricular block and died due to sudden exacerbation of heart failure. Of 7 patients with a root abscess in Group A, 4 (57%) had postoperative valve dehiscence (1 symptomatic, 3 asymptomatic).

Discussion

Since Wallace et al[25] reported the first case of aortic valve replacement in active infective endocarditis in 1965, the role of surgery in the management of this condition has become increasingly important. Valve replacement appears to have contributed to an improved survival rate[10,26] particularly in those patients

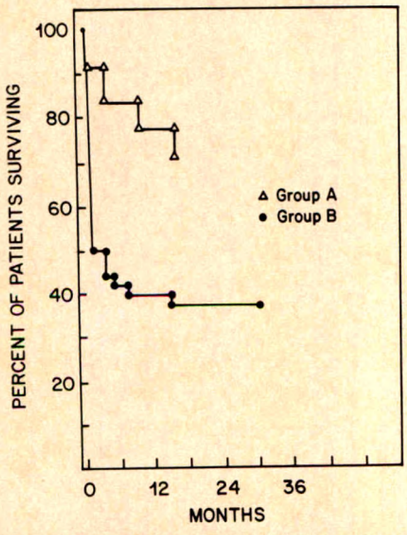

FIGURE 1. Plot of the cumulative hospital and long-term survival rate of all patients in Groups A and B. Plots are extended until the last death in each group. The overall survival rate for patients in Group A is significantly better than that for patients in Group B (p = 0.0004).

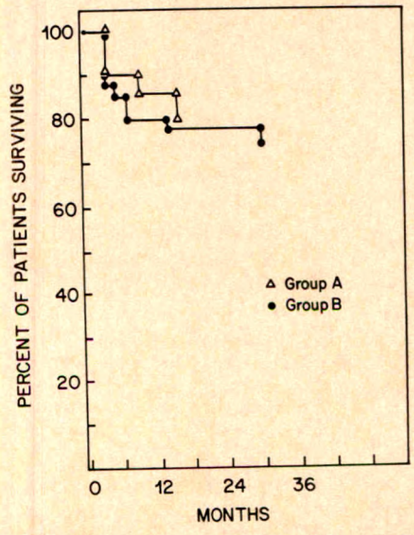

FIGURE 2. Plot of long-term survival rate of patients in Groups A and B who survived the hospital admission. Plots are extended until the last death in each group. There is no significant difference between the 2 groups in the survival rates after discharge (p = 0.624).

with congestive heart failure,[10] in whom the mortality rate when treated medically is 79 to 89%.[27] The magnitude of the improvement in survival rate, both short- and long-term, afforded by surgical intervention is, however, unclear. This study compares the results of surgical and medical therapy of active infective endocarditis at a single institution in patients matched for severity of disease. This was possible because of a generally conservative approach to surgical therapy on the part of internists together with delays in advising surgery due to institution of further medical measures. A sizable population of 85 patients (Group B) satisfying criteria for severe and progressive heart failure, persistent infection, pericarditis, or root abscess had baseline characteristics similar to a surgical group of 23 cases (Group A).

The data presented here demonstrate that surgery in these patients with active infective endocarditis results in a significantly improved hospital mortality rate (9 versus 51%, $p < 0.001$) and that any difference in cumulative long-term survival is largely due to the favorable effect of surgery during the initial hospitalization period. The hospital mortality in this series for patients undergoing valve replacement during active endocarditis (9%) is comparable to the mortality rate in patients undergoing elective aortic (4%)[28] or mitral (7%)[29] valve replacement. Surgery significantly reduced the hospital mortality rate in patients with congestive heart failure only, from 56 to 11%. Although there were no hospital deaths in patients with persistent infection in Group A as compared with a mortality rate of 20% in Group B, the absolute numbers of patients here were too small to make meaningful comparisons.

All patients in Group A and Group B satisfied the stated criteria for severity of illness. There are, however, inherent difficulties in defining more accurately the severity of, for example, congestive heart failure in individual cases. We cannot therefore exclude that individual differences in severity of the various indications within the groups accounted for some of the differences in hospital and long-term mortality rates.

The low yield of organisms from blood cultures in infective endocarditis in this series is in keeping with the overall experience at our institution and consistent with Cherubin and Neu's[4] statement that "in a considerable proportion of cases an organism cannot be cultured by conventional means." In a collective review of all cases of endocarditis at our institution from 1971 to 1980, cultures were persistently negative in 103 of 252 cases (41%) (unpublished data). This is comparable to the 13 to 50%[8,10,11,15,30] incidence of persistently negative cultures quoted in other series. Failure to culture organisms in this and other series may be related to antibiotic therapy before admission, possibly to poor technique in obtaining blood culture samples in individual cases,[31] and to failure to routinely aerate 1 culture bottle.[31] In those patients with culture-negative endocarditis in this series, the diagnosis was confirmed in each case at surgery. In addition, postmortem examination, performed in 31 of the 43 patients (72%) who died in Group B, confirmed infective endocarditis in every case. No patient was referred to surgery with an incorrect diagnosis of infective endocarditis. Our small experience with fungal endocarditis, in contrast to that of Boyd et al[14] is certainly due to the very low incidence of intravenous narcotic abuse locally.

As has been demonstrated before,[8,10,13,15] the risk of infection of prosthetic material sutured into the site of active infection, although contrary to fundamental surgical principles, is small in this situation. Twenty-seven prosthetic valves were implanted in 23 patients during the active stage of infective endocarditis. Only 3 of these patients (13%) had an early recurrence. We attribute this success to detailed attention to radical excision of infected tissue.[8,9] We concur with others[9] that the extent of valvular and perivalvular destruction rarely precludes successful valve replacement. The extent and severity of the infective process did not prohibit valve replacement in any instance when required, despite the presence of 7 root abscesses and extensive double valve disease in 4 patients in this series.

Two subsets of patients at high risk of having postoperative complications have been identified. The first is the group of patients with uncontrolled infection. All 3 patients with an early recurrence of infection had persistent sepsis despite antibiotic therapy for at least 21 days before surgery. This long time period may have allowed spread of infection from the valve itself, the initial site of infection,[32] to the perivalvular inflammatory tissue not excised at surgery. This nidus, generally resistant to antibiotic therapy,[6] might then infect the prosthetic valve. The other subset of high-risk patients are those with aortic root abscesses. Of 7 such patients, 4 (57%) had prosthetic valve dehiscence. This complication was clearly not related to reinfection, but to the edematous and friable nature of tissue into which holding sutures were placed.

The literature is divided as to whether unoperated aortic valve infection carries a worse prognosis than mitral valve infection.[1,33–35] In this series, patients with aortic valve involvement treated medically had a higher long-term mortality rate than those with mitral valve endocarditis. We concur with others,[15] therefore, that surgery should be considered earlier in those with aortic valve infection.

This study has demonstrated the feasibility of operating upon severely ill patients with systemic hypotension and confusion unresponsive to pressor agents. The removal of a septic focus and the dramatic correction of the cause of severe hemodynamic embarrassment in otherwise relatively healthy myocardium are major factors contributing to this improved survival rate with surgery.

Cardiac catheterization during active endocarditis carried no additional risk, thereby confirming the observations of others[17] in this regard. Fears of dislodgement and embolization of vegetations during catheterization[9,36,37] proved unfounded. However, while some reports[6,17,38] testify to the diagnostic usefulness of this procedure in infective endocarditis, others are less enthusiastic.[9,36] In this series, preoperative cardiac catheterization was only of limited value. We therefore recommend that while catheterization can and should be performed before nonemergency surgery with min-

imal additional risk, it should not delay surgery when required urgently and immediately. The course of infective endocarditis is extremely variable, but the subjective sensation of dyspnea at rest or on minimal effort is an excellent marker of even insidious hemodynamic deterioration. While cardiac catheterization is a valuable comfirmatory and diagnostic tool in this setting, we and others[9] believe that, irrespective of the stage of activity of the infective process, definite and progressive symptoms of heart failure should be the cornerstone on which the decision-making process regarding surgery should be built. Procrastination in replacing cardiac valves at this point, in an attempt to stabilize heart failure by medical therapy, to complete or alter antibiotic therapy preoperatively, or both, is usually disastrous.[8,10,36,37]

We conclude that surgery is superior to medical management in patients with active infective endocarditis experiencing progressive class III and IV (New York Heart Association[18]) heart failure. Although numbers were too small to draw conclusions about patients with persistent infection after 21 days of antibiotic therapy, patients should undergo surgery earlier rather than later to prevent postoperative recurrence of infection. Patients with aortic valve involvement treated medically have a poor long-term prognosis; this can be substantially improved by surgical therapy. Patients with aortic valve involvement who have a root abscess are, however, at considerable risk of having both early and late postoperative paravalvular regurgitation. Although cardiac catheterization should be performed in the nonemergency situation, we agree with others[9,36] that it is not essential when immediate surgery is required.

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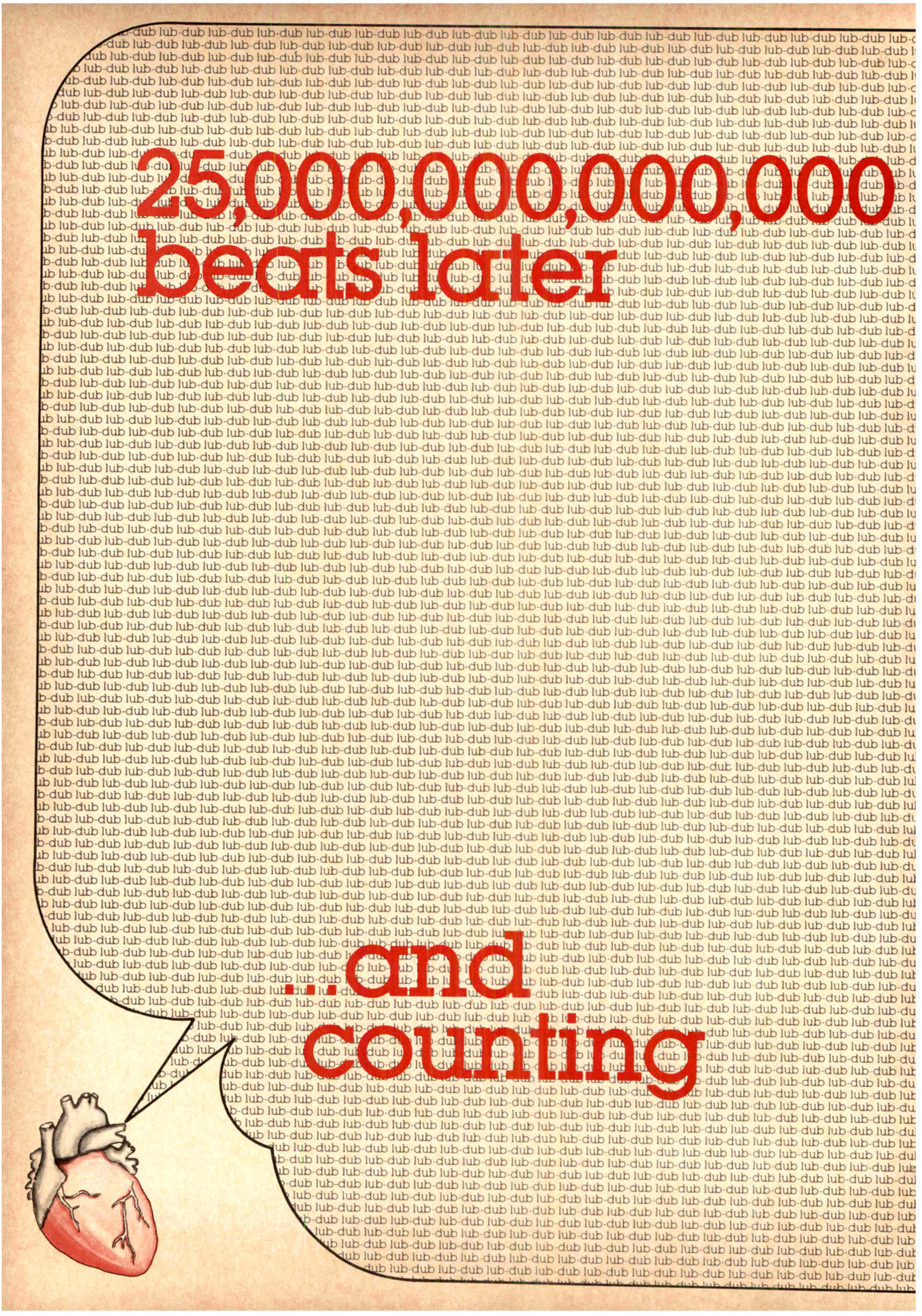
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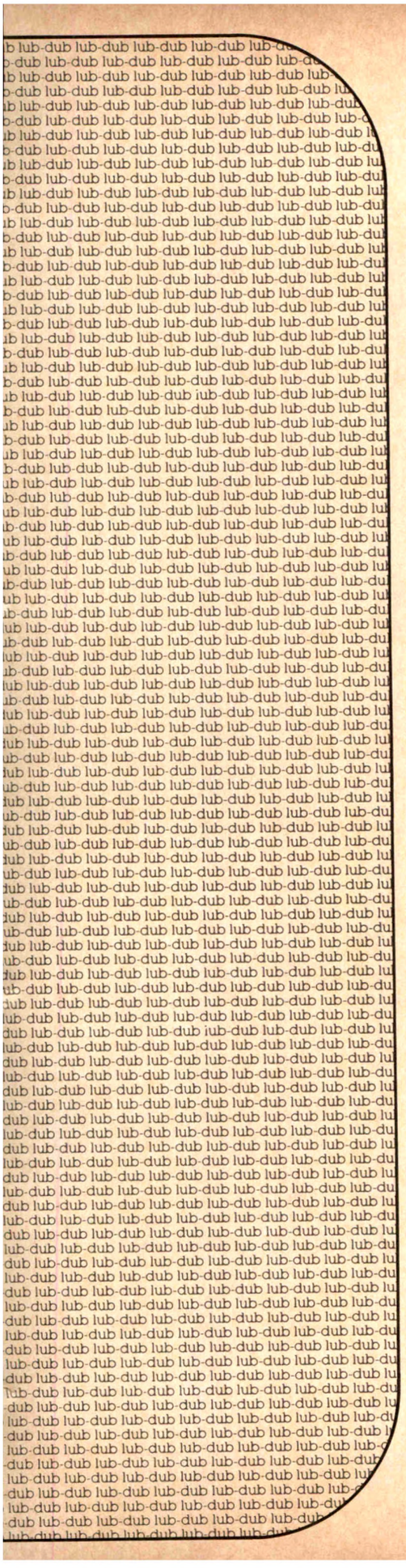

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The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs for overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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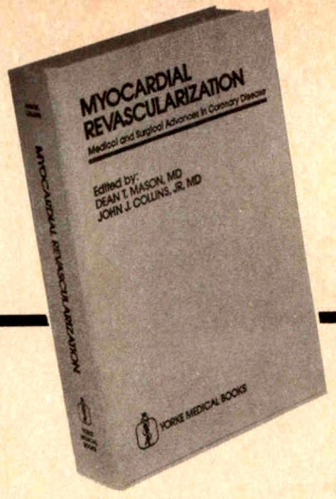

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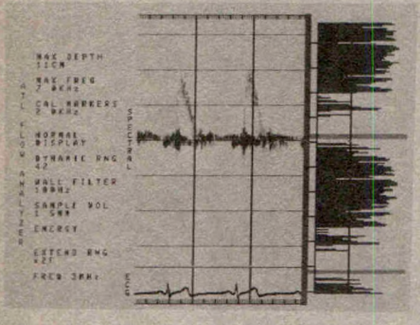

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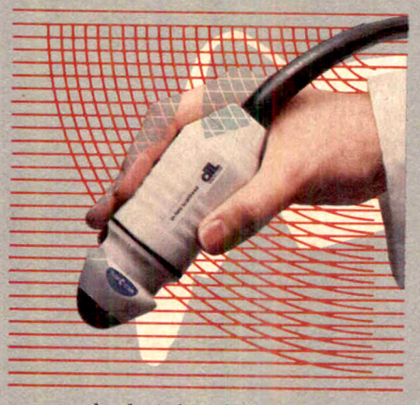

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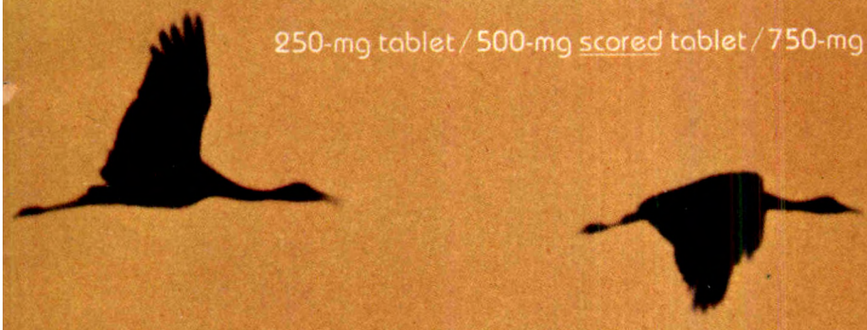

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The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: Procan SR 250 mg (green, film-coated tablet. P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet. P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet. P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).

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Cardiac Disease After Radiation Therapy for Hodgkin's Disease: Analysis of 48 Patients

MARK M. APPLEFELD, MD, and PETER H. WIERNIK, MD

Occult or overt but delayed cardiac disease after thoracic radiotherapy for Hodgkin's disease may be common. Detailed cardiac evaluations were performed in 48 patients with Hodgkin's disease at risk a mean of 97 months after radiotherapy. The study protocol included echocardiography, gated radionuclide ventriculography, and cardiac catheterization. Cardiac disease was found in 46 patients (96%) and included constrictive or occult constrictive pericarditis (24 patients), an abnormal hemodynamic response to a fluid challenge (14 patients), coronary artery disease (6 patients), and left ventricular dysfunction (2 patients). Most patients (53%) had normal echocardiograms. Gated blood pool radionuclide angiocardiography was performed in 42 patients. Excluding patients with occlusive coronary artery disease, the left ventricular ejection fraction at rest (mean 59%) and during exercise (mean 69%) was within normal limits. Congestive heart failure occurred in 2 patients. Six patients had pericardiectomy for constrictive pericarditis and 3 patients had coronary artery bypass surgery for coronary artery disease. Thus (1) delayed cardiac disease after radiotherapy is common, (2) chronic pericardial disorders are the most frequent manifestations of this disease, and (3) the prognosis for patients who have radiation-induced cardiac disease is generally favorable.

> It is proposed that cardiac damage (from radiation therapy)—particularly acute and chronic pericarditis—is more frequent and significant than is generally recognized.
>
> Cohn et al[1]

After its discovery by Roentgen in 1896, the x-ray was first used to treat Hodgkin's disease (HD) and other lymphomas by Pusey[2] in 1902. Advances in technology with the introduction of x-ray equipment able to deliver progressively higher beam energies, a clearer understanding of the biologic behavior of HD, and the pioneering work of Gilbert[3] and Kaplan[4] in planning appropriate treatment fields and radiation doses have each led to control (and in many patients, cure) of HD. As patients with HD have achieved extended survival, physicians responsible for their care have noted late-appearing complications of its treatment. Thus, hypothyroidism, gonadal insufficiency and sterility, and second malignancies are recognized complications of either radiotherapy alone or of combined radiotherapy-chemotherapy in patients with HD. Although earlier reports called attention to cardiac disease complicating radiation therapy,[1,5] its frequency was uncertain and usually manifested by an effusive pericarditis which uncommonly caused pericardial constriction.[5] Based on previous experience,[6,7] we believed that radiation therapy caused delayed cardiac disease more frequently and initiated a study to test this hypothesis.

From the Department of Medicine (Division of Cardiology), and the University of Maryland Cancer Center, the University of Maryland Hospital, Baltimore, Maryland. Manuscript received December 17, 1982; revised manuscript received February 24, 1983, accepted February 25, 1983.

Address for reprints: Mark M. Applefeld, MD, Division of Cardiology, University of Maryland Hospital, 22 South Greene Street, Baltimore, Maryland 21201. .

Method

Of 48 patients studied, 44 are from a cohort of 83 patients with HD who were given mantle radiotherapy before 1977 by either a 4 mV linear accelerator or cobalt-60 source. Details of radiotherapy at other centers were unavailable for 4 patients. In most patients, the technique of "anterior weighting" was used in the mantle. This results in an increased cardiac dose of radiation when compared with current methods.[7] Briefly, an anterior thoracic field of 200 to 250 rads/day for 5 days per week (total mid-plane dose 3,000 to 3,600 rads *or* total anterior dose 4,000 rads) was given over 4 weeks. Either during or after the anterior field, a posterior field was applied, giving a total mid-plane dose of 4,000 rads. Purposeful cardiac shielding was not used in these patients. Indeed, in most of them, 60 to 70% of the cardiac volume received the calculated radiation dose. These 48 patients are seen at the University of Maryland Cancer Center (formerly the Baltimore Cancer Research Center).

These patients were 11 to 60 years old (mean 25) when radiotherapy was given and 18 to 68 years of age (mean 33) when studied 37 to 172 months (mean 97) after the treatment. No patient had other diseases (such as hypertension, connective tissue disorders, prior myopericarditis) known to affect the heart. Thirty patients had chemotherapy (usually nitrogen mustard, vincristine, procarbazine, and prednisone given in 6 monthly cycles) after radiation therapy. Ten patients had an effusive pericarditis during the first 36 months after radiotherapy; 4 required a pericardial window to relieve cardiac tamponade. A viral origin was not confirmed in any of these 10 patients.

TABLE I Patient Classification

	Patients	
	n	%
Constrictive pericarditis	11	23
Occult constrictive pericarditis	13	27
Abnormal hemodynamic response	14	29
Coronary artery disease	6	12
Left ventricular dysfunction	2	4
Normal	2	4

TABLE II Radionuclide Angiocardiography in 41 Patients

	Mean Left Ventricular Ejection Fraction (%)
All Patients	
Rest	57
Exercise	66
Patients With Coronary Artery Disease Deleted	
Rest	59
Exercise	70

Fifteen patients were referred for evaluation of specific cardiac symptoms or signs. These included effort dyspnea (9 patients), angina pectoris and previous myocardial infarction (2 patients each), and an abnormal electrocardiogram and unexplained pleural effusions and hepatomegaly (1 patient each). Thirty-three patients were recruited during their annual evaluation at our center based solely upon their willingness to participate in this study. Of these 33 patients, 18 had mild and 4 had moderate effort dyspnea; 11 were asymptomatic.

The study protocol included M-mode echocardiography (47 patients), equilibrium gated radionuclide angiocardiography (42 patients), and graded treadmill exercise test (2 patients). Right heart catheterizations (usually with a fluid challenge of 1 liter of normal saline solution given intravenously over 8 to 10 minutes[6,8]) were performed in 41 patients; 5 patients had coronary cineangiography. Two patients did not have catheterization. There was no morbidity or mortality from this protocol.

Catheterizations were performed percutaneously after informed consent. Right heart pressures were measured during a rapid pullback (that is, within 10 to 15 seconds) from the pulmonary capillary wedge to right atrium. After catheterization, constrictive pericarditis was diagnosed if there was equalization (within 6 mm Hg) of right heart diastolic pressures and a ratio of pulmonary artery systolic-to-right atrial mean pressure of <3.5 to 1.[9] Most patients also had a dip-plateau configuration in the right ventricular diastolic pressure curve and an absence of respiratory variation in the right atrial mean pressure. Constrictive pericarditis was confirmed at surgery in 6 patients and at autopsy in 1 patient. If right heart diastolic pressures were normal at rest but criteria for constrictive pericarditis were fulfilled after the fluid challenge, occult constrictive pericarditis was diagnosed.[8] If criteria for occult constrictive pericarditis were not met but the diastolic pressures increased by >3 mm Hg after fluid challenge, the hemodynamic response was deemed abnormal.[8] Left ventricular dysfunction was diagnosed when the resting mean pulmonary capillary wedge pressure was elevated (that is, >15 mm Hg) and left ventricular contractility was either regionally or globally abnormal in the absence of angina pectoris or S-T segment depression during exercise. Coronary artery disease was diagnosed by finding coronary artery obstructions (>50%) in 3 patients with angina pectoris and in 1 patient with constrictive pericarditis. In another patient, minor irregularities were found in the right coronary artery 2 months after a proven acute inferior myocardial infarction. Coronary artery disease was suspected in 1 patient who had 2 mm S-T segment depression and left ventricular regional wall motion abnormalities in the absence of chest pain during exercise.

Results

After study, patients were classified as having constrictive or occult constrictive pericarditis, an abnormal hemodynamic response, coronary artery disease, left ventricular dysfunction, or a normal evaluation (Table I). Only 1 patient had more than 1 type of cardiac disease. Thus, among 48 patients with HD, 46 (96%) were found to have cardiac disease when evaluated an average of 97 months after completion of radiotherapy. Of the 2 "normal" patients, 1 had declined cardiac catheterization; the other died from HD and had no cardiac disease evident at necropsy.

Echocardiograms were performed in 47 patients using a 2.25 MHz focused transducer and standard scanning techniques. Paradoxic motion of the interventricular septum was found in 11 patients (23%), 6 with constrictive and 3 with occult constrictive pericarditis. Abnormal diastolic interventricular septal motion was not observed in any patient. A thickened pericardium was noted in 5 patients, 2 each with constrictive and occult constrictive pericarditis and 1 with an abnormal hemodynamic response. Four patients had pericardial effusions; 3 were small and 1 was moderate in size. The echocardiogram was normal in 25 patients (53%).

Forty-one patients had gated radionuclide cardiac studies (Table II). Symptom-limited upright bicycle exercise was performed in 5 patients; it was performed in the supine position (for technical reasons) in 35 patients. One patient had a resting study only. We consider the left ventricular ejection fraction by this technique to be normal if it is ≥45% at rest and if, during exercise, it increases by >8%. The left ventricular ejection fraction was abnormal at rest and during exercise in 7 (17%) patients each. Abnormal resting and exercise gated cardiac studies were present in 3 and 2 patients, respectively, with proven or suspected coronary artery disease. When these 5 patients (in whom abnormal gated cardiac studies might be expected because of their coronary artery disease) were excluded, the left ventricular ejection fractions at rest and during exercise in this patient population were normal (Table II).

Five patients had coronary artery disease; in a sixth, it was suspected when 2 mm S-T segment depression and left ventricular regional wall motion abnormalities developed during exercise. Among the former 5 patients, 4 had high-grade (that is, >75%) coronary artery stenoses. Three had coronary bypass surgery; 2 had a good clinical result and 1 died from sepsis after operation at another center. One patient died from a pulmonary embolus 2 months after an acute myocardial infarction. Marked adventitial fibrosis of the anterior descending and right coronary arteries were noted at necropsy. A fifth patient had minor right coronary artery irregularities and a left ventricular aneurysm 2 months after an acute inferior myocardial infarction..

Of 11 patients with constrictive pericarditis, 6 had a pericardiectomy for disabling effort dyspnea, or right heart failure, or both. The surgical result was good in 3 patients; 2 patients have postoperative hemodynamic findings of visceral pericardial constriction, restrictive cardiomyopathy, or both. One patient died from HD after pericardiectomy. Pericardiectomy was not performed in 5 patients. One patient has died from HD; the other 4 remain stable during a follow-up period extending to 3 years. None of the 13 patients with occult constrictive pericarditis have had pericardiectomy, as their symptoms were not incapacitating.

Discussion

Radiotherapy with or without combination chemotherapy is effective in curing many patients with HD. With the benefit of cure has come increasing recognition of the late-appearing complications arising from the treatment of HD. We believe that delayed-appearing radiation-induced cardiac disease is more common than previously recognized. Thus, we found cardiac disease in 46 of 48 (96%) at risk HD patients who were studied a mean of 97 months after treatment.

It is appropriate to consider whether the method of radiotherapy used in our patients is responsible for their unusually high incidence of cardiac disease. Certainly, a higher cardiac dose[7] of radiation was given when compared with patients treated at other centers where purposeful cardiac shielding[10] or parallel opposing port fields[7] are used. Several comments should be made. First, our radiotherapy method was not unique, that is, other centers used similar methods in the same era. Second, it is uncertain to what extent our treatment method influenced our results. To our knowledge, centers using other radiotherapy methods have neither confirmed nor refuted our findings by an equally detailed cardiac analysis of their patients. Such analyses seem appropriate. Further, at least 3 other reports[11–13] have described significant alterations in cardiac structure, function, or both after radiotherapy.

Some of our patients have abnormal left ventricular contractility by gated blood pool studies. This observation is in keeping with that of others.[12,13] Since constrictive pericarditis does not commonly affect left ventricular contractility, we believe these abnormalities may be indicative of myocardial fibrosis. However, we agree with Brosius et al[11] that clinical consequences of this presumed myocardial fibrosis seem to be unimportant. Whether this observation will remain valid as these patients age is uncertain. Indeed, cardiac changes induced by the aging process[14] may be synergistic with those caused by radiotherapy.[15] In turn, these changes may lead to significant disability among these patients in future years.

Evidence supporting the relation between radiation and cardiac disease in our patients comes from several sources. First, no patient had other diseases known to affect the pericardium or myocardium. Although 10 patients had acute pericarditis after radiation, a viral origin was not confirmed in any of them. Second, 2 patients with coronary artery disease had vascular changes consistent with effects of ionizing radiation. One had intimal proliferation; the other had coronary arterial narrowing by severe adventitial fibrosis. Third, the cardiac disease observed in our patients fits a pattern previously ascribed to radiotherapy.[1,2,10–13] Thus, although evidence *conclusively* linking cardiac disease to thoracic radiotherapy is unavailable in many of our patients, this relationship seems very compelling.

In conclusion, radiation-induced cardiac disease occurs frequently. This is certainly true among patients who have had "anterior weighted" mantle radiotherapy.[16] Whether this will also be the experience in patients treated by parallel opposing port mantle radiotherapy remains to be determined. Preliminary observations at our center are equivocal in this regard. It would seem that purposeful cardiac shielding during the mantle field should reduce the incidence of radiation-induced cardiac disease. This hypothesis has not yet been critically tested. The risk of developing cardiac disease extends for an indefinite period after radiotherapy and it is unknown to what extent the aging process modifies this risk. Pericardial abnormalities remain the most common manifestation of radiation-induced cardiac disease. Altered left ventricular contractility is not rare among such patients, although it seems to be unimportant clinically. Despite the occurrence of abnormalities in cardiac structure and function after mantle radiotherapy, the long-term prognosis for patients who have radiation-induced cardiac disease is generally favorable.

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Contrasting Acute Effects of Vasodilators (Nitroglycerin, Nitroprusside, and Hydralazine) on Right Ventricular Performance in Patients With Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension: A Combined Radionuclide-Hemodynamic Study

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Fourteen patients with chronic obstructive pulmonary disease, mild to moderate pulmonary hypertension, and diminished right ventricular (RV) ejection fraction were studied acutely with use of a combined radionuclide-hemodynamic approach to assess and contrast the effects of 3 vasodilators on RV performance and central hemodynamic function. *Nitroglycerin* significantly decreased mean right atrial pressure, RV end-diastolic volume index, mean pulmonary artery pressure, cardiac index, and arterial oxygen tension, but did not affect pulmonary vascular resistance index and increased RV ejection fraction. *Nitroprusside* had similar effects on mean right atrial pressure, RV end-diastolic volume index, mean pulmonary artery pressure, cardiac index, and arterial oxygen tension, but also mildly decreased pulmonary vascular resistance index and did not alter RV ejection fraction. In contrast, *hydralazine* decreased pulmonary vascular resistance index and increased cardiac index and RV ejection fraction. The increase in ejection fraction correlated well with the decrease in pulmonary vascular resistance. These data suggest that in patients with mild to moderate secondary pulmonary hypertension, acute administration of hydralazine results in a substantial improvement in RV performance by virtue of decreasing pulmonary vascular resistance. In contrast, nitroglycerin and nitroprusside demonstrate predominant effects that reduce preload, cardiac index, and arterial oxygen tension. Based on these data, afterload reduction with vasodilators such as hydralazine may be potentially useful in selected patients with pulmonary disease and secondary pulmonary hypertension and appear preferable to agents that primarily reduce preload. Further long-term studies are necessary to establish therapeutic efficacy.

By virtue of altering the loading conditions faced by the left ventricle, vasodilators have been shown to result in direct hemodynamic and clinical benefit in the treatment of patients with left ventricular failure.[1,2] These drugs may exert their primary effect on either the systemic resistance or capacitance vasculature, or both. The effects of vasodilators on right ventricular (RV) performance in patients with pulmonary hypertension and RV dysfunction have not been investigated extensively. To date, studies have focused for the most part on primary pulmonary hypertension and have emphasized measurement of intravascular pressures rather than direct assessment of volumetric changes and RV performance.[3–11] The objective of the present study was to evaluate the effects of 3 vasodilators, each with a different primary mode of action, on RV performance and central hemodynamic function with use of a combined radionuclide and hemodynamic approach. A selected homogeneous group of patients with chronic obstructive pulmonary disease, secondary pulmonary

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TABLE I Clinical and Pulmonary Function Data

Case	Age (yr) & Sex	FEV_1 (liters)	FVC (liters)	FEV_1/FVC (%)	RV/TLC (%)	DLCO (ml/min/mm Hg)	Arterial Blood Gas		
							PO_2 (mm Hg)	pH	PCO_2 (mm Hg)
1	50F	0.53 (19%)	1.05 (29%)	51	51	7.0 (35%)	80	7.36	56
2*	62M	1.77 (67%)	3.57 (94%)	50	32	14.0 (52%)	58	7.53	31
3	67M	1.01 (38%)	2.57 (67%)	39	39	13.1 (53%)	56	7.52	31
4	63F	0.85 (47%)	1.53 (62%)	56	48	3.0 (16%)	55	7.46	39
5	33M	1.66 (40%)	3.42 (64%)	49	37	35.0 (111%)	83	7.41	33
6	56M	0.53 (16%)	1.31 (29%)	40	66	13.7 (48%)	73	7.39	41
7	64M	0.71 (22%)	1.98 (48%)	39	43	5.4 (24%)	70	7.50	37
8	66M	1.44 (45%)	2.97 (27%)	43	51	4.5 (20%)	45	7.46	31
9	61M	0.94 (32%)	2.57 (63%)	37	45	. . .	64	7.43	36
10	61M	1.15 (50%)	2.52 (79%)	46	46	23.3 (91%)	86	7.56	35
11	53M	0.73 (22%)	1.57 (38%)	51	72	9.7 (41%)	72	7.41	37
12*	68M	1.41 (51%)	2.83 (70%)	50	44	20.3 (82%)	68	7.41	40
13	64M	0.75 (23%)	1.56 (61%)	48	43	5.4 (24%)	63	7.42	37
14	77M	0.83 (38%)	2.04 (61%)	41	58	23.3 (72%)	47	7.38	45
Mean	60	1.02 (36%)	2.25 (60%)	45	48	13.7 (52%)	66	7.45	38
±	±	±	±	±	±	±	±	±	±
SD	10	0.40 (15%)	0.79 (18%)	6	11	9.5 (30%)	13	0.06	7

* Patients with moderate obstructive airway disease; all others had severe airway obstruction.[15] DLCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PCO_2 = arterial carbon dioxide tension; % = percent of predicted; PO_2 = arterial oxygen tension; RV = residual volume; SD = standard deviation; TLC = total lung capacity.

hypertension, and decreased resting RV ejection fraction was studied. To assess the acute effects of preload and impedance reduction on the pressure-overloaded right ventricle, the following drugs were administered: *nitroglycerin*, which primarily decreases venous return thereby altering RV preload[11,12]; *hydralazine*, which decreases pulmonary vascular resistance thereby altering impedance to RV ejection[7–9,13]; and *nitroprusside*, a drug with combined effects.[14]

Methods

Patient group: A group of 14 patients with clinically stable chronic obstructive pulmonary disease was studied. Major criteria for inclusion in this study were the demonstration of abnormal right ventricular ejection fraction (<45%) and mild to moderate elevation of mean pulmonary artery pressure (≥20 mm Hg) at rest; both criteria were fulfilled by all 14 patients. Patients were selected from a larger population of well-categorized subjects in a respiratory disease clinic. All had symptoms of dyspnea, but the major factor for initial consideration for study was an abnormal RV ejection fraction at rest. Patients were relatively uniform with respect to hemodynamic and ventilatory characteristics (Tables I to III). Although 2 patients had had a previous episode of right heart failure, all were stable and without clinical evidence of heart failure at the time of study. None had right ventricular hypertrophy by conventional electrocardiographic criteria. No patient had clinical or electrocardiographic evidence of systemic hypertension, valvular heart disease, coronary artery disease, or primary myocardial disease. None manifested clinical or hemodynamic evidence of tricuspid regurgitation as defined by typical auscultatory findings or large V waves in the right atrial pressure tracing, respectively. Three patients had an unexplained mild decrease in left ventricular ejection fraction (45 to 48%, normal ≥55%); the remaining patients had normal left ventricular ejection fraction. Based on pulmonary function testing, 12 patients had severe and 2 moderately severe chronic obstructive pulmonary disease.[15] None had evidence of reversible bronchoconstriction (150 μg of isoproterenol [Isuprel®, Mistometer, Winthrop Laboratories]). Twelve patients were men and 2 women. Their ages ranged from 33 to 77 years (mean 58).

Radionuclide technique: First-pass radionuclide angiocardiograms were obtained with the patient in the anterior position using a computerized multicrystal scintillation camera (Baird-Atomic System-77, Bedford, Massachusetts).[16,17] Six to 10 mCi of high specific activity technetium-99m diethylenetriamine pentaacetic acid was injected into the superior vena cava through the proximal part of a balloon-tipped pulmonary artery catheter. This radioactive tracer is cleared relatively rapidly from the blood pool by renal excretion. Thirty minutes were allowed to pass between placement of the intravascular catheters and the onset of the study, thereby minimizing any potential hemodynamic effects related to anxiety or pain associated with catheter placement. A minimum of 30 to 45 minutes transpired between repeat radionuclide injections. RV and left ventricular ejection fractions were measured from time-activity curves according to standard techniques.[16,17] Reproducibility of these measurements in stable patients is within ± 5% (absolute ejection fraction units) for both right and left ventricular ejection fractions.

Hemodynamic technique: A catheter was placed percutaneously into the radial artery, and a balloon-tipped thermodilution pulmonary artery catheter was passed through an antecubital vein cutdown to the pulmonary artery. Intravascular pressures recorded from the fluid-filled catheters were measured using a Bentley transducer positioned 5 cm below the angle of Lewis and recorded on an Electronics for Medicine recorder (Echo IV). Systolic and diastolic pulmonary artery pressures (PAP) and pulmonary capillary wedge pressures (PCWP) and mean right atrial pressure were measured by averaging pressures over at least 2 respiratory cycles, and mean pressures were obtained by electronic integration. All pressure transducers were "zeroed" to air and calibrations checked with a mercury sphygnomanometer. Cardiac output was measured in triplicate by the thermodilution technique, with injection of iced saline solution and a commercially available microprocessor (Edwards Laboratories, model 9520A). The stated results represent the average of 3 clustered measurements with less than 10% variation. Derived values

TABLE II Acute Hemodynamic Effects of Sublingual Nitroglycerin

Case		HR (beats/min)	CI (liters/min/m²)	RAP (mm Hg)	$\overline{PAP}$ (mm Hg)	PPAP (mm Hg)	PWP (mm Hg)	SAP (mm Hg)	PVRI (dynes·s·cm⁻⁵·m²)	SVRI	RVEDVI (ml/m²)	RVEF (%)	LVEF (%)	RVSWI (g·m/m²)
1	C	100	2.7	14	43	63	13	100	948	2,963	93	29	69	16
	N	115	2.2	. . .	37	52	10	80	873	2,909	43	44	75	10
2	C	82	2.3	8	25	37	12	105	452	3,652	70	40	83	10
	N	89	2.1	. . .	16	23	8	83	343	3,162	60	40	75	5
3	C	80	3.2	10	30	41	9	95	545	2,375	95	42	63	16
	N	85	2.8	. . .	25	34	6	85	542	2,429	75	44	69	11
4	C	65	3.4	10	30	45	12	95	424	2,235	149	35	52	21
	N	71	2.7	6	24	33	8	90	474	2,667	95	40	56	12
5	C	67	3.5	8	24	34	11	65	297	1,486	118	44	58	17
	N	70	2.7	4	16	21	9	62	207	1,837	89	44	60	9
6	C	80	4.6	10	26	35	15	135	191	2,435	153	38	68	21
	N	88	3.5	6	21	30	9	120	274	2,742	93	43	65	11
7	C	82	1.9	5	22	31	8	115	589	4,842	58	40	57	7
	N	92	1.4	2	17	23	5	105	743	6,000	35	43	63	4
8	C	60	2.5	8	40	60	12	90	896	2,880	145	29	47	23
	N	63	2.0	4	30	45	8	70	880	2,800	86	37	54	13
M ± SD	C	77 ± 12	3.0 ± 0.8	9 ± 3	30 ± 7	43 ± 11	12 ± 2	100 ± 20	540 ± 249	2,859 ± 953	110 ± 34	37 ± 5	62 ± 1	16 ± 5
	N	84 ± 15	2.4 ± 0.6	4 ± 2	23 ± 7	33 ± 9	8 ± 2	87 ± 17	542 ± 248	3,068 ± 1,167	72 ± 22	42 ± 2	65 ± 7	9 ± 3
	p	<0.001	<0.005	<0.001	<0.001	<0.001	<0.001	<0.005	NS	NS	<0.005	<0.01	NS	<0.001

P values are derived from paired *t* tests.
C = control value; CI = cardiac index; HR = heart rate; LVEF = left ventricular ejection fraction; M ± SD = mean ± standard deviation; N = nitroglycerin; NS = not significant; $\overline{PAP}$ = mean pulmonary artery pressure; PPAP = peak systolic pulmonary artery pressure; PWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVSWI = right ventricular stroke work index; SAP = systemic arterial pressure; SVRI = systemic vascular resistance index.

TABLE III Effects of Nitroglycerin, Hydralazine, and Nitroprusside on Gas Exchange Parameters

Case		PaO_2 (mm Hg)	$PMVO_2$ (mm Hg)	$DAaO_2$ (mm HG)
1	C	80	. . .	138
	N	73	. . .	144
2	C	58	31	53
	N	52	27	73
3	C	56	35	55
	N	57	29	61
4	C	55	39	46
	N	51	31	53
5	C	83	49	26
	N	82	47	32
6	C	73	31	26
	N	63	29	41
7	C	70	34	34
	N	64	33	41
8	C	45	25	66
	N	41	23	72
M ± SD	C	65 ± 13	35 ± 7	56 ± 34
	N	60 ± 12	31 ± 7	65 ± 33
p		<0.01	<0.05	<0.005
9	C	62	30	44
	H	65	39	45
10	C	93	38	18
	H	92	40	16
11	C	76	34	29
	H	78	38	42
12	C	70	38	31
	H	70	42	36
13	C	60	33	45
	H	68	38	43
14	C	49	32	49
	H	48	33	56
M ± SD	C	68 ± 15	34 ± 3	36 ± 12
	H	70 ± 15	39 ± 3	40 ± 14
p		NS	<0.01	NS
9	C	64	32	41
	NP	58	30	48
10	C	86	37	20
	NP	84	37	22
11	C	72	34	32
	NP	70	32	35
12	C	68	38	32
	NP	65	35	40
13	C	63	24	41
	NP	53	29	52
14	C	49	32	45
	NP	48	30	46
M ± SD	C	67 ± 12	34 ± 3	35 ± 9
	NP	63 ± 13	32 ± 3	41 ± 11
p	. . .	<0.05	<0.05	<0.05

P values are derived from paired *t* tests.
$DAaO_2$ = alveolar-arterial oxygen tension difference; H = hydralazine; NP = nitroprusside; PaO_2 = arterial oxygen tension; $PMVO_2$ = mixed venous oxygen tension; other abbreviations as in Table II.

obtained from hemodynamic and radionuclide data either alone or in combination were calculated as follows: cardiac index (liters/min/m²) = cardiac output/body surface area; stroke volume index (ml/m²) = cardiac index/heart rate × 1,000; pulmonary vascular resistance index (dynes·s·cm⁻⁵·m²) = 80 × (mean PAP − mean PCWP)/cardiac index; systemic vascular resistance index (dynes·s·cm⁻⁵·m²) = 80 (mean arterial pressure − mean right atrial pressure)/cardiac index; RV end-diastolic volume index (ml/m²) = stroke volume index/RV ejection fraction; RV end-systolic volume index (ml/m²) = RV end-diastolic volume index − stroke volume index; RV stroke work index (g·m/m²) = mean PAP × stroke volume index × 13.6/1,000.

Arterial and mixed venous oxygen saturations were measured using the Macro Reflexion Oximeter (American Optical,

mm Hg ($p < 0.01$), pulmonary capillary wedge pressure from 14 ± 3 mm Hg to 12 ± 3 mm Hg ($p < 0.05$), systemic arterial pressure from 112 ± 9 to 95 ± 7 mm Hg ($p < 0.001$), pulmonary vascular resistance index from 534 ± 152 to 450 ± 134 dynes·s·cm^{-5}·m^2 ($p < 0.01$) (Fig. 1). Heart rate was unchanged. Cardiac index, RV end-diastolic volume index, pulmonary vascular resistance index, and mean pulmonary artery pressure decreased in each patient. Nitroprusside decreased RV stroke work index (16 ± 5 to 11 ± 4 g·m/m^2, $p < 0.001$). After nitroprusside, there was no significant change in either right or left ventricular ejection fraction (Fig. 2).

Nitroprusside administration resulted in effects on gas exchange similar to nitroglycerin. Nitroprusside widened the alveolar-arterial gradient (35 ± 9 versus 41 ± 11 mm Hg ($p < 0.05$) and decreased arterial oxygen tension from 67 ± 12 to 63 ± 13 mm Hg ($p < 0.025$), and mixed venous oxygen tension from 34 ± 3 to 32 ± 3 mm Hg ($p < 0.025$) (Table III).

Hydralazine (Table V): After administration of hydralazine, there was a significant increase in heart rate from 81 ± 7 to 91 ± 10 beats/min ($p < 0.025$) and an increase in cardiac index from 2.4 ± 0.4 to 4.1 ± 0.7 liters/min/m^2 ($p < 0.05$). The pulmonary vascular resistance decreased substantially from 594 ± 232 to 362 ± 179 dynes·s·cm^{-5}·m^2 ($p < 0.01$); the pulmonary vascular resistance index decreased in all patients (Fig. 1). The decrease in pulmonary vascular resistance index correlated with baseline pulmonary vascular resistance ($r = 0.89$, $p < 0.01$), indicating that the greatest change occurred in those with highest initial levels. There was no significant change in mean right atrial pressure, RV end-diastolic volume index, mean or peak pulmonary artery pressure, or mean pulmonary capillary wedge pressure. RV stroke work index increased from 14.5 ± 4 to 20 ± 7 g·m/m^2 ($p < 0.05$). After administration of hydralazine, there also was a significant decrease in systemic arterial pressure from 110 ± 4 to 91 ± 8 mm Hg ($p < 0.01$).

After hydralazine administration there was a substantial increase in RV ejection fraction from 37 ± 5 to 45 ± 6% ($p < 0.01$) and in left ventricular ejection fraction from 63 ± 15 to 74 ± 13% ($p < 0.005$) (Fig. 2). However, the augmentation in ejection fraction for the right and left ventricles did not correlate ($r = 0.14$), indicating that improvement in RV performance was not dependent on augmentation of left ventricular function. Hydralazine increased the RV ejection fraction in all patients, and the increase in RV ejection fraction correlated well with the change in pulmonary vascular resistance index ($r = 0.89$, $p < 0.01$), but not with the baseline RV ejection fraction ($r = 0.05$) or changes in heart rate ($r = 0.04$). There was no significant correlation with the change in RV ejection fraction and the change in RV end-diastolic volume index ($r = 0.55$, difference not significant). Thus, the increase in RV ejection fraction after hydralazine was related well to the change in pulmonary vascular resistance but was independent of changes in heart rate (suggesting no baroreceptor reflex input) and changes in RV volume. A concomitant increase in stroke work index was observed.

After hydralazine there was no significant change in arterial oxygen tension or the alveolar-arterial oxygen tension gradient. However, there was a significant increase in mixed venous oxygen tension from 34 ± 3 to 39 ± 3 mm Hg ($p < 0.01$) (Table III).

RV stroke work: The interaction of RV stroke work index and end-diastolic volume for each of the 3 vasodilators is illustrated in Figure 3. Although hydralazine resulted in an increase in stroke work with no change in ventricular volume, nitroglycerin and nitroprusside resulted in a decrease in both stroke work and end-diastolic volume.

Discussion

The success encountered in using vasodilators for the treatment of left ventricular failure has increased interest in the application of the same principles and use of some of the same drugs for the treatment of the failing pressure-overloaded right ventricle.[4–11] The results of the present investigation indicate that acute administration of primary arterial vasodilators, such as hydralazine, result in substantial improvement in RV performance by virtue of decreasing pulmonary vascular resistance and impedance to ejection. Furthermore, in contrast to the other vasodilators studied, hydralazine increased mixed venous oxygen tension and did not decrease arterial oxygen tension. When coupled with an increase in cardiac output, this results in an increase in systemic oxygen delivery, a potentially beneficial effect, particularly in this disease state.

In contrast to hydralazine, the effects of nitroglycerin and nitroprusside were less salutary. Both drugs affect a significant reduction in venous return as a result of venous pooling, thereby decreasing preload. Nitroglycerin exhibited no effect on pulmonary vascular resistance, whereas nitroprusside resulted in a modest decrease. Nitroglycerin resulted in a small but significant increase in RV ejection fraction, whereas nitroprusside did not. This improvement in ejection fraction may have been the result of a secondary baroreceptor reflex response rather than a primary effect due to alterations in loading conditions of the right ventricle.

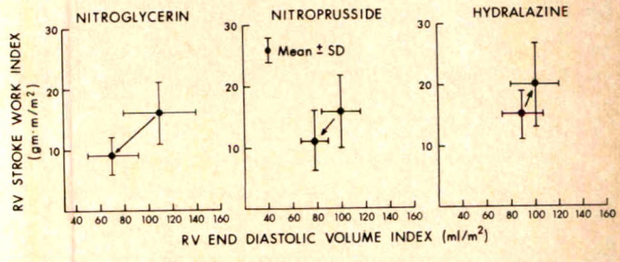

FIGURE 3. Relationship between right ventricular (RV) end-diastolic volume index and right ventricular stroke work index after administration of nitroglycerin, nitroprusside, and hydralazine. Nitroglycerin and nitroprusside produced statistically significant decreases in both right ventricular end-diastolic volume index and stroke work index. In contrast, hydralazine caused no change in right ventricular end-diastolic volume and a significant increment in right ventricular stroke work index. Results are expressed as mean ± standard deviation (SD).

Both nitroglycerin and nitroprusside resulted in a decrease in RV stroke work index and cardiac index. In addition, both agents induced a decrease in arterial oxygen tension and mixed venous oxygen and a widening of the alveolar-arterial oxygen tension difference. This phenomenon, noted previously with both drugs, coupled with a decrease in cardiac output, resulted in a substantial decrease in systemic oxygen delivery,[11,18,19] which may have important deleterious effects.[20]

On the basis of these data, it appears that in selected patients with mild to moderate secondary pulmonary hypertension, pulmonary arterial vasodilators may be potentially useful. This corroborates previous hemodynamic observations of Rubin and Peter[7,8] concerning hydralazine administration in primary pulmonary hypertension and in cor pulmonale both at rest and during exercise. However, not all patients will respond favorably to hydralazine and hemodynamic and functional characterization may help define those who will respond.[9,21] Recently, Lupi-Herrera et al[9] reported on the effects of hydralazine therapy in 12 patients with pulmonary hypertension of unknown cause. They subclassified patients into responders and nonresponders. Of relevance to the present data, hydralazine responders had baseline mean pulmonary artery pressures and resistances that were comparable with those observed in the patients in our study. Pulmonary artery pressure in nonresponders was significantly higher than observed in responders; all responders had baseline mean pulmonary artery pressures $\leq$46 mm Hg, whereas all nonresponders had baseline pressures $\geq$63 mm Hg. Of equal importance, acute hemodynamic results appeared to reflect more long-term effects. The results must be juxtaposed against the recent report of Hermiller et al[22] who noted no beneficial effects from hydralazine in a group of patients with primary pulmonary hypertension.

In contrast, agents with a more prominent preload effect, such as nitrates or nitroprusside, may result in potentially deleterious consequences with respect to both central hemodynamics and oxygen delivery. The latter observations highlight important differences between vasodilator therapy for diseases primarily affecting either the left or right ventricle. These differing therapeutic responses result from differences in the functional anatomy of the 2 chambers, the more marked afterload dependence of the right ventricle, and the basic pathophysiological mechanisms responsible for impaired ventricular performance in these differing disease states.[23–25]

Several additional points deserve emphasis. First, these observations were made only in the acute state. The patients studied were all stable at the time of evaluation and none manifested clinical evidence of significant heart failure. Additional long-term studies in a broader clinical spectrum of patients are necessary to establish therapeutic efficacy and clinical relevance. Second, these observations were obtained only in the resting supine state. It is important as well to demonstrate appropriate therapeutic responses under stress conditions such as exercise. RV ejection fraction may respond inadequately during exercise in patients with chronic obstructive pulmonary disease.[26] Third, vasodilator therapy also can have untoward effects in individual patients with pulmonary hypertension and result in systemic hypotension as well as a drug-induced increase in pulmonary artery pressure. This was demonstrated by Cohen and Kronzon[27] after administration of phentolamine. The mechanism of this phenomenon may involve insufficient pulmonary arterial vasodilation and predominating effects on the systemic circulation with either an uncompensated decrease in systemic vascular resistance, an increase in venous return, or both. Inadequate pulmonary vasodilation may occur when reversible vasoconstriction is not present and advanced pathologic lesions which are pharmacologically insensitive have developed in the pulmonary circulation. Recently, data have been presented indicating that hydralazine may be of little benefit and may frequently result in deleterious effects in patients with moderately severe primary and secondary pulmonary hypertension.[21] Differences between these results and those of our study as well as those of Rubin and Peter[7,8] and Lupi-Hererra et al[9] may be based on patient selection and the specific diseases evaluated. Nevertheless, the administration of vasodilator agents in patients with pulmonary hypertension clearly requires careful monitoring of intravascular pressures and RV performance in order to optimize therapy and detect unsuspected untoward effects. In the resting state, RV pump function correlates well with pulmonary artery pressure.[24] However, as evidenced by the data of this study, drug-induced changes in RV ejection fraction may not always reflect changes in pulmonary artery pressure, resistance, or flow. Ejection fraction may be augmented without a change in pulmonary resistance (as evidenced by the response to nitroglycerin in our patients). Fourth, additional pharmacologic agents may become available for the treatment of both primary and secondary pulmonary hypertension. Recently, Simonneau et al[10] demonstrated that nifedipine inhibits hypoxic pulmonary vasoconstriction in patients with acute respiratory failure. In this laboratory we have shown recently that terbutaline, a beta-2 agonist, exerts favorable effects on RV function similar to hydralazine in patients with pulmonary disease, pulmonary hypertension, and RV dysfunction.[28] These effects can at least in part be related to terbutaline-induced decreases in pulmonary vascular resistance. Clearly, these classes of drugs as well as arterial vasodilators and inotropic agents such as digitalis[29] will require more in-depth follow-up studies.

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Reoperation for Isthmic Coarctation of the Aorta: Follow-Up of 26 Patients

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Twenty-six patients underwent reoperation for coarctation of the aorta (C of A) between 1972 and 1980. Most patients (73%) had undergone primary repair in infancy. The interval to reoperation was 5 months to 18 years (mean 8.2 years). Indications for reoperation included symptoms in 4, exercise systemic hypertension in 1, electrocardiographic changes of left ventricular strain in 1, arm hypertension in 21, and a C of A gradient at rest >30 mm Hg in all. Surgical procedures included patch aortoplasty (16 patients), bypass graft (6 patients), left subclavian angioplasty (3 patients), and end-to-end anastomosis (1 patient). There were no operative complications or mortality. There was 1 late death from aortic valve disease. Duration of follow-up in the remaining 25 patients was 2 weeks to 7 years (mean 2.5 years). All patients are asymptomatic. C of A gradients were significantly reduced from 30 to 132 mm Hg (mean 56) preoperatively to 0 to 48 mm Hg (mean 15) postoperatively. Right arm systolic blood pressure also was significantly improved from 120 to 237 mm Hg (mean 153) preoperatively to 100 to 160 mm Hg (mean 124) postoperatively. Systemic systolic hypertension persisted in 5 of 25 (20%). It is concluded that C of A reoperation is a low risk procedure that improves symptoms and reduces C of A gradient and arm blood pressure. However, systolic hypertension does not always resolve postoperatively. Patch aortoplasty appears to be a safe and effective surgical approach.

Although repair of isthmic coarctation of the aorta (C of A) is a common and safe procedure, inadequate relief or restenosis is not unusual. Several long-term follow-up studies have documented an incidence of 5 to 11% of persistent or recurrent C of A pressure gradients after primary repair in childhood,[1–4] with a substantially higher incidence, approximately 33%, after repair in infancy.[3–9] In some patients, the residual C of A has required a second operation to relieve the obstruction. The results of reoperation for C of A have been less well documented.[10,11] Therefore, we retrospectively reviewed our experience with reoperation for C of A, specifically assessing the results in terms of successful relief of residual obstruction and systemic hypertension, as well as the morbidity and mortality of reoperation.

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Methods

Between 1972 and 1980, 26 patients underwent a second operation for repair of C of A at our institution. Patients with complex intracardiac defects or those with interruption of the aortic arch were excluded. The charts were reviewed for the clinical information, catheterization data, and operative notes from both operations. The clinical status, arm blood pressure, and pressure gradients across the C of A before reoperation were recorded. If cardiac catheterization was performed within 6 months before surgery, the C of A gradient was defined as the pullback pressure differential. Otherwise, the C of A gradient was taken as the difference between the right arm and leg cuff pressures recorded immediately preoperatively. Right arm blood pressure and C of A gradients were noted at the time of discharge from the hospital, when available, and at subsequent follow-up visits. Postoperative clinical status was determined from clinic notes. Follow-up treadmill studies and cardiac catheterization results are included, when available.

Patients with right arm systolic blood pressure, on the most recent reading, exceeding the 95% percentile for age[12,13] were considered hypertensive. Statistical significance was evaluated by the t test for paired observations.

Primary repair: Of the 26 patients, 21 had their initial C of A surgery at our institution between 1954 and 1979. Five

TABLE I Primary Repair

Case	Sex & Age (mo)	Associated Conditions	C of A Surgery	Δ (mm Hg) Immediately Postoperatively	Δ >20 mm Hg First Noted Postoperatively
1	F, 7 day	PDA	End-to-end*	...	...
2	M, 7 days	PDA	End-to-end	25	D/C
3	F, 0.7	PDA	End-to-end	...	3 mo
4	M, 1	PDA	End-to end	...	7 yr
5	M, 1.2	0	Blalock Park	...	1 mo
6	F, 2	0	End-to-end	55	D/C
7	M, 2	PDA	NA*	...	...
8	M, 3	MR	End-to-end	40	D/C
9	M, 5	0	End-to-end	10	5 mo
10	F, 11	PDA	End-to-end	65	D/C
11	F, 6 days	VSD, PDA	End-to-end*	...	...
12	M, 7 days	VSD, PDA, ASD	End-to-end	...	...
13	F, 12 days	VSD, PDA, ASD	LSCA	...	...
14	F, 0.5	VSD, ASD	NA	38	D/C
15	M, 0.5	VSD, PDA	LSCA	38	D/C
16	F, 1	VSD, PDA	LSCA	...	3 mo
17	F, 3	VSD, PDA	End-to-end	50	D/C
18	F, 3	VSD, PDA	End-to-end	...	2 mo
19	M, 5	VSD, PDA	End-to-end*	...	5 mo
20	M, 60	William's, PPS	Bypass graft	...	1 mo
21	F, 72	0	End-to-end	0	8 yr
22	M, 72	0	End-to-end	0	3 mo
23	F, 60	Turner's	End-to-end*	...	...
24	F, 84	Turner's, PDA	End-to-end	0	6 yr
25	M, 96	0	Bypass graft	35	D/C
26	M, 108	William's	Bypass graft	35	D/C

* Surgery performed elsewhere.
Δ = pressure gradient between arms and legs; ASD = atrial septal defect; C of A = coarctation of the aorta; D/C = at hospital discharge; LSCA = left subclavian angioplasty; MR = mitral regurgitation; NA = data not available; PDA = patent ductus arteriosus; PPS = peripheral pulmonary stenosis; VSD = ventricular septal defect.

had primary repair performed elsewhere and full details were not always available. Altogether, 6 institutions and 10 different surgeons were involved. The details of the initial repair are summarized in Table I. There were 13 female and 13 male patients aged 6 days to 9 years (mean 2.1 ± 3.0 years) at the time of primary repair. Of the 26 patients, 19 (73%) were operated on at <1 year of age. Associated cardiovascular defects, primarily found in infants, included patent ductus arteriosus (15 patients), ventricular septal defect (9 patients), atrial septal defect (3 patients), mitral regurgitation (1 patient), and peripheral pulmonary stenosis (1 patient). Four of the 7 children who were >5 years of age at the time of primary repair had dysmorphic syndromes (William's syndrome, 2 patients; Turner's syndrome, 2 patients).

Initial surgical repair included resection with end-to-end anastomosis (17 patients), left subclavian angioplasty (3 patients), Blalock-Park procedure (2 patients), bypass graft from ascending to descending aorta (2 patients), and unknown (2 patients). Blood pressure recordings, available on hospital discharge after primary repair in 12 patients, revealed a C of A gradient (≥20 mm Hg) in 8 of 8 infants and in 9 of 12 of the entire group. Several other patients had paired pressures first recorded in follow-up clinic visits. Taken together, these documented a residual gradient ≥20 mm Hg within 6 months of surgery in 13 of 14 infants (93%) and in 17 of 20 of the entire group (85%). The gradients in 3 others were first detected at 6.3, 7.0, and 8.0 years postoperatively. Serial follow-up data were unavailable in the remaining 6 patients.

Reoperation: The details of reoperation are summarized in Table II. Age at reoperation ranged from 5 months to 20.8 years (mean 10.3 ± 6.2 years). The interval between the 2 operations was 5 months to 17.6 years (mean 8.2 ± 5.0 years). There was no difference in the interval to reoperation in the infant group (8.0 ± 5.5 years) versus the older children (8.7 ± 3.8 years).

The indications for reoperation in patients >1 year of age were symptoms in 3 (headaches in 2, claudication in 1), electrocardiographic changes of left ventricular strain in 1, exercise hypertension in 1, and upper extremity hypertension with a gradient of ≥30 mm Hg in the remaining 17. Reoperation was performed within the first year of life in 4 patients because of severe systolic hypertension (>200 mm Hg) in 3 and congestive heart failure in 1.

Cardiac catheterization and angiography were performed in 25 patients preoperatively and revealed discrete narrowing in 20, a long segment C of A in 2, multiple discrete areas of narrowing in 1, acquired isthmic aortic atresia in 1, and no discrete narrowing in 1.

Surgical approaches for secondary repair included patch angioplasty (16 patients), bypass graft (6 patients), left subclavian angioplasty (3 patients), and end-to-end anastomosis (1 patient). There were no operative complications or mortality.

Results

Follow-up: Follow-up results of reoperation are summarized in Table III. There was 1 late death from aortic regurgitation (case 20) 7 years after C of A reoperation. Follow-up in the remaining 25 patients ranged from 2 weeks to 7 years (mean 2.5 ± 2.2 years). All symptoms that were present preoperatively resolved. One patient developed mild hoarseness. The electrocardiographic changes of left ventricular strain that were present preoperatively in 1 individual persisted postoperatively.

Follow-up catheterization was performed in 3 patients primarily to evaluate associated congenital heart defects. Interestingly, one patient (patient 6) was found

TABLE II Reoperation

Case	Age (yr)	Interval (yr)	Preoperative BP (mm Hg)	Preoperative Δ (mm Hg)	Angiography			Surgery
					C of A Discrete	VSD	Other	
1	9 mo	9 mo	237/107*	132*	+	0	0	Patch
2	4	4	120/70	30	. . .	. . .	. . .	LSCA
3	14	14	148/64	50	+	0	0	Patch
4	18	18	128/	38*	+	0	0	Patch
5	12	12	160/104	70	+	0	0	Patch
6	8	7	130/*	52*	+	0	0	Patch
7	15	15	140/52	42*	+	0	0	Patch
8	15	15	184/70	70	+	0	MR	Bypass graft
9	14	14	161/62*	60*	+	+	PS, AR	Patch
10	6	6	130/72	35*	+	0	0	Bypass graft
11	6 mo	6 mo	124/60*	64*	+	+		End-to-end
12	8	8	140/60	36	0‡	0	0	Patch
13	5 mo	5 mo	210/85*	125*	+†	0	0	Patch
14	6	6	135/80	55	+	0	0	Patch
15	9 mo	9 mo	200/*	90*	+	0	0	Patch
16	8	8	138/90*	33*	+	0	0	Patch
17	8	7	146/90	53*	+	0	0	Bypass graft
18	16	16	150/80	50	+	+	0	Bypass
19	6	6	130/80*	34*	0‡	0	0	LSCA
20	13	8	170/110	80	+	0	0	Bypass graft
21	18	12	160/60	30	0	0	0	Patch
22	18	12	150/80	40	+	0	0	Patch
23	10	4	130/80	60	+	0	0	LSCA
24	18	10	140/100	40	+	0	0	Patch
25	12	4	125/80*	48*	+	0	0	Patch
26	21	12	190/80	50	+	0	0	Bypass graft

* Catheter determined.
† Acquired total occlusion (atresia).
‡ Long segment coarctation of the aorta.
AR = aortic regurgitation; PS = pulmonary stenosis. Other abbreviations as in Table I.

to have a C of A proximal to the left subclavian artery that was not present on the angiogram before reoperation.

Coarctation gradient: The change in the C of A gradient from the preoperative period to the most recent follow-up examination is diagrammed in Figure 1. Preoperative C of A gradients at rest ranged from 30 to 132 mm Hg (mean 56 ± 26). On follow-up, the gradients were significantly reduced to 0 to 48 mm Hg (mean 15 ± 15), $p < 0.001$. There was a trivial resting gradient (0 to 10 mm Hg) in 10 (40%), a mild residual gradient (11 to 20 mm Hg) in 9 (36%), and a moderate residual gradient (30 to 48 mm Hg) in 6 (24%). The gradient was improved in 23, unchanged in 1, and increased in 1. Five of the 6 patients with moderate residual gradients underwent patch aortoplasty procedures, but this association was not significant because 16 of 26 patients (62%) in this series had this type of secondary repair.

Although the follow-up period is still relatively short (mean 2.5 ± 2.2 years), there has been no significant change in the postoperative C of A gradients from the time of hospital discharge (mean 11.6 ± 11.0 mm Hg) to the latest follow-up evaluation (15.3 ± 14.5 mm Hg). Gradients assessed during this period actually decreased in 9, increased in 11, and were unchanged in 3.

Hypertension: The distribution of systolic blood pressure in the preoperative period and on the most recent follow-up examination are diagrammed in Figure 2, showing age-adjusted norms. Systolic blood pressure in the right arm preoperatively ranged from 120 to 237 mm Hg (mean 153 ± 30). On follow-up, the pressures were significantly reduced, ranging from 100 to 150 mm Hg (mean 124 ± 14), $p < 0.005$. Although improved, systolic hypertension persisted in 5 of 25 (20%). Three patients continue to be treated with antihypertensive medications. The follow-up C of A gradients in the 5 hypertensive patients were 0, 2, 16, 20, and 30 mm Hg. Therefore, 2 patients have remained hypertensive despite no residual C of A gradient.

Discussion

Age distribution: In the past decade, several long-term follow-up studies have substantiated the problem of persistent or recurrent C of A after initial repair. The reported incidence has been 5 to 11% in children who had repair beyond the first year of life.[1–4] The incidence is substantially higher in the infant group (0 to 60%),[3–9] with most figures clustering about 20 to 36%. Thus, it is not surprising that reoperation is more commonly performed in children whose initial repair was performed during infancy. Infants comprised 73% of the patients in our series and 68% among the 44 children in 7 previously reported series[10,11,14–18] of reoperation for C of A.

In our series, no patients were between 1 and 5 years of age at the time of primary repair. This finding most likely reflects our experience that there is a bimodal distribution of surgery with infants with complicated coarctations frequently requiring surgery in the first year because of refractory congestive heart failure and the remainder electively repaired before starting school.

Causes of residual gradient: The residual obstruction found in postoperative coarctation patients has been attributed to several different causes, including inadequate relief, retention of abnormal ductal tissue,[13,29] insufficient growth of the anastomotic site,[22,23] fibrosis of the suture line,[23] and thrombosis and calcification of bypass grafts. Histologic data are unfortunately lacking because resection of the coarctation segment is rarely performed at the time of reoperation. Further discussion of etiologic factors remains essentially speculative on the basis of the chronologic reappearance of the coarctation gradient after the initial repair.

Multiple mechanisms are probably involved. The follow-up data that were available from the first operation documented a C of A coarctation gradient at hospital discharge in 9 of 12 patients (75%) of our group and within 6 months in 17 of 20 (85%). This finding suggests that the residual gradient was due in part to inadequate relief. The majority of these early gradients continued to increase substantially with time, suggesting progressive fibrosis or inadequate growth of the suture line, or both, as contributing factors.

Of some interest is that 57% of the children who were >5 years of age at the initial repair and required reoperation had either Turner or William's syndrome. Perhaps there is an intrinsic defect in the vascular connective tissue elements in these individuals that predisposes them to recurrent problems with C of A.

Residual hypertension: There has been much concern about residual hypertension after primary C

TABLE III Follow-Up

Case	Age (yr)	Interval (mo)	BP (mm Hg)	Δ (mm Hg)
1	1	4	120/...	12
2	5	14	124/88*	16
3	17	40	120/78	0
4	18	2	110/50	0
5	12	5	124/80	10
6	14	78	140/78*	20
7	18	24	138/74	38
8	17	23	130/70	0
9	21	85	150/70	40
10	7	14	125/75*	30
11	4	39	100/...	20†
12	8	1	100/60	5
13	3	31	120/*	0
14	7	14	105/56	35†
15	2	18	100/70	0
16	12	40	120/60	48
17	13	68	125/70	20†
18	21	66	130/72	15
19	6	3	118/70*	2
20	...	...	...	...
21	18	2	150/60	30
22	20	19	130/80	0
23	14	48	125/70	15
24	19	20	130/75	0
25	13	12	130/60	15
26	27	78	140/80	12

* Hypertensive.
† Catheter determined.

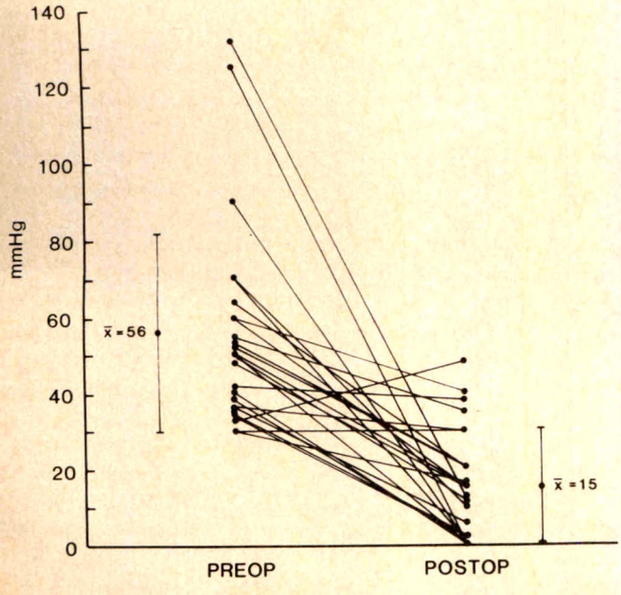

FIGURE 1. Coarctation pressure gradient at rest before reoperation (PREOP) and on follow-up evaluation (POSTOP) after reoperation for coarctation of the aorta.

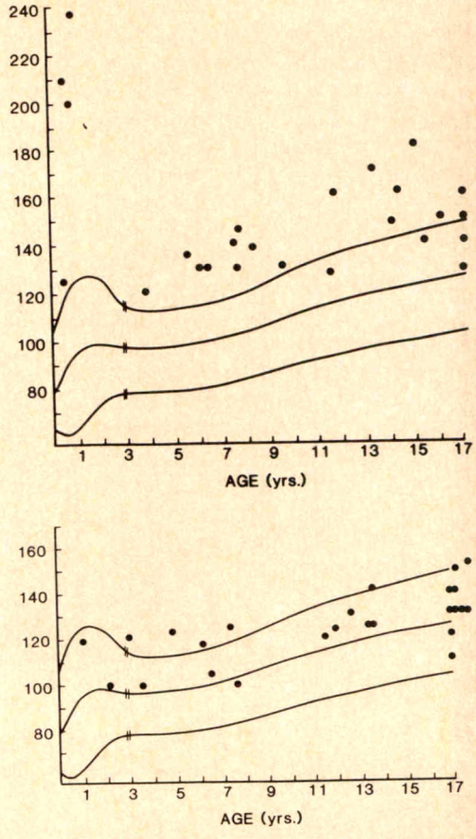

FIGURE 2. Top, arm systolic blood pressure at rest before reoperation for coartation of the aorta. Percentiles (5-50-95) are based on data of Nadas and Fyler[13] for 0 to 3 years of age and those of the National Institutes of Health Task Force[12] for those >3 years of age. **Bottom,** arm systolic blood pressure at rest on follow-up evaluation after reoperation for coarctation of the aorta.

of A repair. Figures for persistent hypertension, unexplained by a residual C of A coarctation gradient, vary with age of repair and duration of follow-up and have been reported at 8.4,[1] 12.3,[3] and 31%.[19] Unfortunately, different norms and cutoffs have also been applied. Liberthson et al[20] showed that persistent postoperative hypertension was progressively more common in patients who had repair at advancing ages from early childhood through adulthood. Nanton and Olley[2] demonstrated that in children aged 1 to 15 years, the earlier the age at operation, the greater the reduction in blood pressure.

In this series, after reoperation for C of A, 5 patients (20%) have persistent systolic hypertension. However, this does not correlate with age at primary or secondary repair. All 5 of these patients had initial repair in infancy (mean age 0.31 ± 0.37 years), with the interval to reoperation (4.7 ± 2.8 years) being shorter than that for the entire group (8.2 ± 5.0 years). The persistent hypertension cannot always be explained by residual hemodynamic obstruction. The mean gradient for these 5 patients was 13.6 ± 12.6 mm Hg as opposed to a mean of 15.3 ± 14.5 mm Hg for the entire group. There were no significant differences in preoperative blood pressure or C of A gradient or in the type of surgical repair. The only other long-term follow-up study on reoperation[10] reported a 29% incidence of postoperative hypertension.

Exercise testing: Exercise testing is useful in evaluating results after primary repair of C of A.[21] In this series, 8 patients had exercise studies after reoperation. Seven had graded treadmill studies according to the standard Bruce protocol, with arm and leg cuff pressures assessed immediately after peak exercise. The other was exercised during cardiac catheterization with the ergometer bicycle with the patient in the supine position. All 8 patients had a significant increase in C of A gradients, including the 3 individuals with no demonstrable gradient at rest. In addition, 2 patients had significant systolic hypertension of 190 and 210 mm Hg. Exercise testing can provide valuable information in counseling such patients to avoid strenuous activity.

Surgical results: Previously reported mortality rates for reoperation in C of A differ widely, but appear to be improving with time: Cerilli and Lauridsen 50% (1965),[18] Khoury and Hawes 17% (1968),[7] Ibarra-Perez et al 15% (1969),[11] Tawes et al 10% (1969),[8] Castaneda and Norwood 7.3% (1979),[16] and Beekman et al 4.8% (1982).[10] There was no morbidity or mortality in this series. (The previously published series by Castaneda combines his experience from 2 institutions and therefore has some overlaps with this series.)

Different approaches have been proposed for repair of coarctation of the aorta including resection,[22] patch aortoplasy,[23] bypass grafting,[24] and left subclavian angioplasty.[25] Balloon dilatation has recently been proposed as an alternative approach. Although transluminal angioplasty was reportedly successful in 1 infant with restenosis after C of A repair,[26] experimental studies question its feasibility.[27] Thus far, we have had no experience with this technique. Because of the theoretical problem of limited growth of circumferential suture lines, we currently favor the use of subclavian angioplasty in primary repair of C of A in neonates and infants and a Dacron® patch aortoplasty in older children. The approach to reoperation is primarily governed by anatomy. This series demonstrates that patch aortoplasty, when feasible, gives satisfactory results with low mortality. Because of potential long-term problems associated with patch grafting,[23] further follow-up is important.

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Subxyphoid 2-Dimensional Echocardiographic Identification Of Left Ventricular Papillary Muscle Anomalies in Complete Common Atrioventricular Canal

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Mitral valve dysfunction is probably the major cause of operative mortality from total repair of complete common atrioventricular (AV) canal in infancy. The presence of a solitary left ventricular (LV) papillary muscle appears to be 1 anatomic factor influencing the success of mitral reconstruction because suturing of the cleft between the superior and inferior components of the anterior mitral leaflet creates a parachute mitral valve deformity, which may result in stenosis or in unduly high tension on the components of the repair. This study reports on (1) the 2-dimensional (2-D) echocardiographic appearance of the LV papillary muscle architecture in patients with complete common AV canal compared with that in normal subjects, and (2) the incidence of solitary LV papillary muscle in patients with complete common AV canal.

Two-dimensional echocardiography was performed in 31 infants with complete common AV canal, 14 normal infants, and 9 infants with a large ventricular septal defect not involving the AV canal region. Of 31 infants with complete common AV canal, 26 (80%) had 2 LV papillary muscles on 2-D echocardiography, 3 (10%) had 3 LV papillary muscles, and 3 (10%) had 1 LV papillary muscle. In patients with 2 LV papillary muscles, the anterolateral papillary muscle was displaced posteriorly compared with that in normal subjects and in patients with ventricular septal defect, whereas the posteromedial papillary muscle was in its normal location.

Among the 25 patients with complete common AV canal with 2 LV papillary muscles, there was 1 operative death. Among the 6 infants with complete common AV canal with LV papillary muscle anomalies, 5 underwent surgical repair with 4 early deaths.

Subxyphoid 2-D echocardiography is a useful technique for evaluating LV papillary muscle architecture in complete common AV canal and permits identification of patients who may be at higher risk for unsuccessful mitral reconstruction.

The operative mortality rate for repair of complete common atrioventricular (AV) canal in patients <2 years of age is 17 to 25%.[1–6] Mitral valve dysfunction is probably the major cause of early postoperative death.[6] At least 4 anatomic factors influence the success of mitral valve reconstruction in complete common AV canal: quantity of AV valve leaflet tissue, the alignment of the common AV valve in relation to the ventricles, the presence or absence of double orifice mitral valve, and the presence or absence of a solitary left ventricular (LV) papillary muscle.[6] Preoperative detection of solitary LV papillary muscle should alert the surgeon to avoid extensive suturing of the "cleft" between the superior and inferior components of the anterior mitral leaflet which results in a parachute mitral deformity.[7,8] Intraoperatively, it is often difficult to examine the LV papillary muscle architecture from the left atrium.

This study reports on (1) the 2-dimensional (2-D) echocardiographic appearance of the LV papillary muscles in complete common AV canal as compared with normal, and (2) the frequency of LV papillary muscle anomalies in patients with complete common AV canal.

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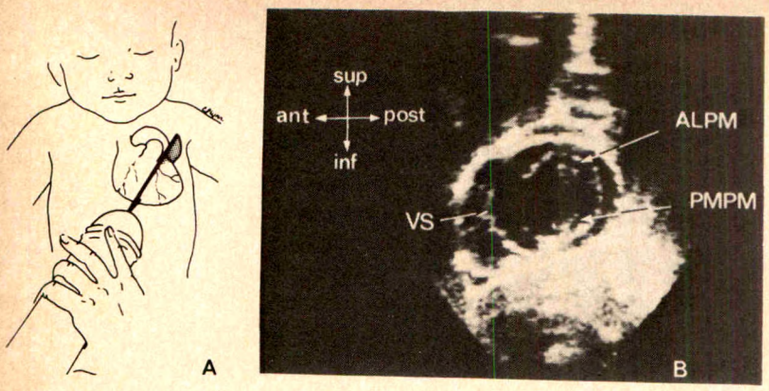

FIGURE 1. Transverse view of the left ventricle. **A,** ultrasound plane used to image the left ventricular papillary muscle architecture at the level of the chordal-papillary muscle junctions. **B,** normal left ventricle using the ultrasound plane shown in **A.** ALPM = anterolateral papillary muscle; ant = anterior; inf = inferior; PMPM = posteromedial papillary muscle; post = posterior; VS = ventricular septum.

Material and Methods

Between January 1, 1977 and July 30, 1980, subxyphoid 2-D echocardiography was performed in 31 patients with the diagnosis of complete common AV canal confirmed at surgery (30) or autopsy (1). Two independent observers reviewed the examinations retrospectively along with those of 14 patients with no known cardiovascular disease (normal control subjects) and 9 patients with nonrestrictive ventricular septal defect confirmed at cardiac catheterization; this defect was confirmed at operation to be conoventricular, membranous, or muscular in location (morbid control subjects).

The 31 patients with complete common AV canal, aged 1 day to 13 months (median 4 months), included 27 with Down's syndrome. None of the 14 normal control subjects (aged 1 day to 22 months [median 17 days]), or the 9 morbid control subjects (aged 7 days to 13 months [median 2 months]) had Down's syndrome.

Subxyphoid 2-D echocardiography was performed using a Picker Echoview 80 CI system with a mechanical sector scanner. The intracardiac structures were displayed with a 45 to 60° sector angle and an image rate of 45 to 60 frames/s. All studies were performed with either a 5 mHz short-focus or 3.5 MHz medium-focus crystal with a 13-mm active element diameter.

The LV papillary muscle architecture was displayed in a subxyphoid transverse plane at the first appearance of the papillary muscles on the base to apex sweep. The number of LV papillary muscles was assessed at this level (chordal-papillary muscle junction) in all patients. The position of the center of each papillary muscle as well as the endocardial position of the anterior and posterior junctions of the ventricular septum with the LV free wall were marked on an acetate overlay for 3 consecutive cardiac cycles at end-diastole (Q wave in the electrocardiogram) (Fig. 1). From these tracings, a perpendicular from the mid-point of the chord connecting the anterior and posterior septum-LV free wall junctions was constructed as a reference line. Lines were then constructed from the origin of the reference line to the centers of the papillary muscles, and the angles between these lines and the reference line were determined (Fig. 2). Angles above the reference line were expressed as negative values and angles below the reference line as positive values. The angles were used as an index of the positions of the papillary muscles on the LV free wall.

All measurements were made by 2 independent observers to assess interobserver variability.

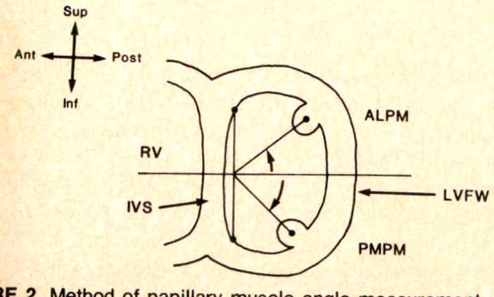

FIGURE 2. Method of papillary muscle angle measurement. A perpendicular passing through the midpoint of the chord connecting the ventricular septum-left ventricular free wall (LVFW) junctions served as a reference line. Lines between the origin of the reference line and the centers of the papillary muscles were then constructed. Angles **(unlabeled arrows)** between these lines and the reference line were determined; angles above the reference line were expressed as negative values, and angles below the reference line as positive values. IVS = interventricular septum; RV = right ventricle; other abbreviations as in Figure 1.

Results

Number of LV papillary muscles: In all cases, the findings of the 2 observers were concordant regarding the number of LV papillary muscles. Of the 31 patients with complete common AV canal, 25 had 2 LV papillary muscles on 2-D echocardiography, 3 had 3 LV papillary muscles, and 3 had a solitary LV papillary muscle (Fig. 3). All 14 normal patients and all 9 patients with ventricular septal defect had 2 LV papillary muscles.

Surgical or autopsy confirmation of the LV papillary muscle anatomy was available in all 3 patients with solitary LV papillary muscle seen on 2-D echocardiography. Of the 3 patients with 3 LV papillary muscles on 2-D echocardiography, there was postmortem confirmation in 2 and no record of surgical observations in the survivor. Of the 25 patients with complete common AV canal with 2 LV papillary muscles on 2-D echocardiography, none of the operative notes for the 23 survivors of repair comment on LV papillary muscle architecture. Autopsy confirmed the presence of 2 LV papillary muscles in the 2 who died.

Positions of left ventricular papillary muscles: The position of the LV papillary muscles could be determined in all 14 control patients and in 21 of the 31 patients with complete common AV canal. In the re-

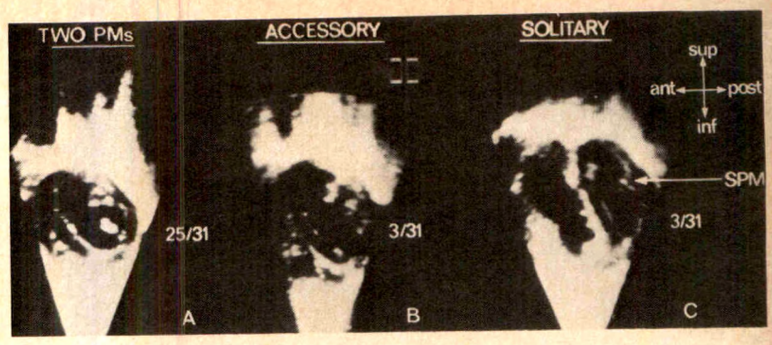

FIGURE 3. Two-dimensional echocardiograms demonstrating the 3 basic types of left ventricular (LV) papillary muscle (PM) morphology in complete common atrioventricular canal. **A,** in patients with complete common atrioventricular canal with 2 LV papillary muscles, the anterolateral papillary muscle is shifted posteriorly and inferiorly compared with that in normal subjects. See also Figure 4. **B,** complete common atrioventricular canal with 3 LV papillary muscles. **C,** complete common atrioventricular canal with solitary LV papillary muscle (SPM). The position of the SPM corresponds closely to the position of the anterolateral papillary muscle in patients with complete common atrioventricular canal and 2 LV papillary muscles.

maining patients with complete common AV canal, the anterior and posterior septum-LV free wall junctions could not be seen simultaneously on an end-diastolic stop frame, making construction of a reference line impossible.

Fifteen of the 21 patients with complete common AV canal in whom LV papillary muscle positions could be measured had 2 LV papillary muscles. The angle of the anterolateral papillary muscle was $-14° \pm 5°$ (mean ± standard deviation), whereas the angle of the posteromedial papillary muscle was $49° \pm 14°$.

The anterolateral papillary muscle position in the 14 normal patients was $-36° \pm 15°$; the posteromedial papillary muscle position was $+44° \pm 9°$.

The anterolateral papillary muscle position in the 9 patients with ventricular septal defect was $-26° \pm 9°$; the posteromedial papillary muscle position was $+44° \pm 11°$.

The maximum difference between the 2 observers for any measurement was 17°, with 92% of the measurements differing by $\leq 10°$.

The anterolateral papillary muscle in patients with complete common AV canal with 2 LV papillary muscles is shifted posteriorly when compared with that in normal subjects ($p < 0.001$, 2-tailed test) or in patients with large ventricular septal defect ($p < 0.001$) (Fig. 4). The position of the posteromedial papillary muscle in patients with complete common AV canal was not significantly different from that in normal subjects ($0.05 < p < 0.10$) or in patients with large ventricular septal defect ($p > 0.10$).

The position of the LV papillary muscles in the 3 patients with complete common AV canal with 3 LV papillary muscles was determined by the same technique. The position of the most superior LV papillary muscle was $-34°$, $-24°$, and 0° in these 3 patients. The position of the "middle" LV papillary muscle was +13°, +8°, and +21°, respectively. The position of the most inferior LV papillary muscle was +41°, +58°, and +38°, respectively.

In the 3 patients with complete common AV canal with solitary LV papillary muscle on 2-D echocardiography, the positions of the papillary muscles were +5°, +9°, and +25°. Thus, the position of the solitary LV papillary muscle corresponds closely to the position of the anterolateral papillary muscle in patients with complete common AV canal with 2 LV papillary muscles (Fig. 3).

Clinical course: Of the 3 patients with complete common AV canal with solitary LV papillary muscle, 1 died during induction of anesthesia before operation. (All other infants with complete common AV canal in this series underwent complete repair including suture of the cleft between the superior and inferior components of the anterior mitral leaflet.) The other 2 patients died early postoperatively. One acutely developed severe mitral regurgitation and died despite emergency mitral valve replacement; the other patient died from LV failure due to LV hypoplasia which was not recognized antemortem. Mild mitral stenosis was documented at early postoperative catheterization. All 3 of the patients with solitary LV papillary muscle had deficient left lateral leaflet tissue, verified by autopsy or surgical observation.

In 1 of the 3 patients with complete common AV canal with 3 LV papillary muscles, the LV papillary muscles coalesced toward the apex into a common base on the LV free wall. This arrangement theoretically functionally approximates a solitary LV papillary muscle. This patient died 10 days after repair because of disruption of the mitral cleft closure confirmed at autopsy. Of the other 2 patients with 3 LV papillary muscles, 1 died after acutely developing severe mitral regurgitation; autopsy revealed partial dehiscence of the anterior mitral leaflet from the septal patch. The remaining patient is alive and apparently well.

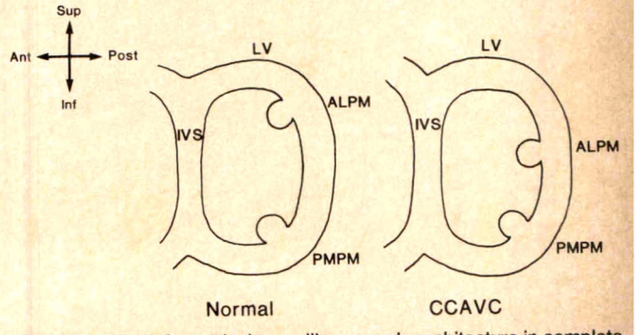

FIGURE 4. The left ventricular papillary muscle architecture in complete common atrioventricular canal (CCAVC) as compared with that in normal subjects. The anterolateral papillary muscle (ALPM) is shifted posteriorly and inferiorly in the CCAVC, whereas the posteromedial papillary muscle (PMPM) is in its usual location. LV = left ventricle; other abbreviations as in Figures 1 and 2.

Among the 25 patients with complete common AV canal with 2 LV papillary muscles, there was 1 operative death and 1 late death. Postmortem examination in both patients demonstrated that the mitral valve reconstruction was intact and did not appear stenotic or regurgitant.

Discussion

Axial angiography using the hepatoclavicular projection[9] has improved our preoperative delineation of several anatomic features relevant to complete common AV canal repair: alignment of the common AV valve in relation to the ventricles, the presence or absence of ventricular hypoplasia, and additional muscular ventricular septal defects. The projection orthogonal to the hepatoclavicular projection outlines the LV papillary muscles in some cases, but adequate visualization cannot always be achieved because of torrential shunting of contrast medium across the ventricular septal defect.

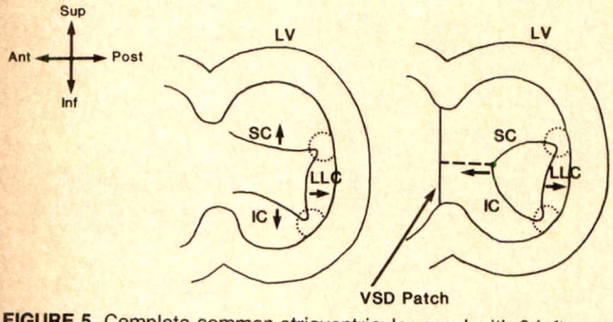

FIGURE 5. Complete common atrioventricular canal with 2 left ventricular papillary muscles pre- and postoperatively. Diagram of a transverse view during diastole at the level of the atrioventricular valve leaflets, the free margins of which are represented by the **solid line.** The papillary muscles are represented by **dotted lines** because they would be visualized in a transverse view at a different level. **Left,** preoperatively, the superior cushion (SC) and inferior cushion (IC) components of the common atrioventricular valve move superiorly and inferiorly, respectively, during valve opening. **Right,** suturing of the cleft during repair converts a trileaflet valve to a bileaflet valve. The 2 components of the anterior mitral leaflet now move anteriorly as a unit during valve opening. The motion of the left lateral cushion (LLC) is undisturbed. VSD = ventricular septal defect; other abbreviations as before.

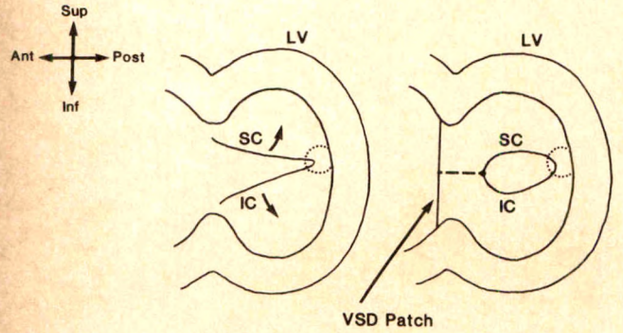

FIGURE 6. Complete common atrioventricular canal with solitary left ventricular papillary muscle pre- and postoperatively. Diagram of a transverse view, during diastole, at the level of the atrioventricular valve leaflets. **Left,** preoperative pattern of movement. The superior cushion (SC) and inferior cushion (IC) components of the common atrioventricular valve move superiorly and inferiorly, respectively, during valve opening. **Right,** suturing of the cleft during repair converts a bileaflet valve to a unileaflet valve (parachute mitral deformity). Abbreviations as before.

Subxyphoid 2-D echocardiography is a useful technique for identifying solitary LV papillary muscle in infants with complete common AV canal. There have not been any false positive diagnoses of solitary LV papillary muscle by 2-D echocardiography because in all such cases surgical observation or autopsy, or both, confirmed the findings. We cannot evaluate the false-negative rate of detecting solitary LV papillary muscle by 2-D echocardiography because all but 2 of the patients with 2 LV papillary muscles on 2-D echocardiography are still alive, and the LV papillary muscle architecture was not commented on in any of the operative reports of these survivors. A prospective series will be needed with systematic surgical observations in order to define the true incidence of solitary LV papillary muscle.

The significance of solitary LV papillary muscle in complete common AV canal lies in the observation that extensive suturing of the "cleft" between the superior and inferior components of the anterior mitral leaflet results in a parachute mitral deformity.[7,8] Suturing of this cleft in complete common AV canal patients with 2 LV papillary muscles converts a "trileaflet" valve into a "bileaflet" valve. The 2 components of the anterior mitral leaflet, which move apart in a superoinferior direction preoperatively, move as a unit in an anteroposterior direction postoperatively. (The motion of the lateral leaflet is undisturbed.) (Fig. 5). In patients with complete common AV canal with a solitary LV papillary muscle, suturing of the cleft converts a functional bileaflet valve to essentially a unileaflet valve (Fig. 6). Whether this parachute mitral deformity results in stenosis or in unduly high tension on the components of the repair should theoretically depend on how extensively the cleft is sutured. Acutely increasing the tension on leaflet tissue or drastically altering the distribution of tension may be major causes of dehiscence of the mitral reconstruction in the early postoperative period. Among the 5 patients with complete common AV canal and LV papillary muscle anomalies who underwent surgery, 4 died in the early postoperative period. Three of the deaths were due to the acute development of severe mitral regurgitation. It is possible that in patients with LV papillary muscle anomalies, dehiscence of the mitral reconstruction may actually be a more common surgical sequela than stenosis.

Carpentier[7] advocated leaving the cleft unsutured, thus preserving the geometry of the pattern of movement of the superior and inferior components of the anterior mitral leaflet and thereby presumably minimizing tension on the reconstructed region. Whether the mitral valve in patients with solitary LV papillary muscle can be satisfactorily repaired by leaving the cleft unsutured is unknown; late postoperative cardiac catheterization data in infants with solitary LV papil-

lary muscle repaired without cleft suture are not yet available.

This study also demonstrates that the anterolateral papillary muscle is situated more posteriorly in patients with complete common AV canal than in normal infants. This posterior displacement is not merely due to the presence of a LV volume overload because the anterolateral papillary muscle in patients with large ventricular septal defect not involving the AV canal region was not displaced posteriorly. The position of the posteromedial papillary muscle in patients with complete common AV canal does not appear to be different from that in normal subjects. Therefore, in patients with complete common AV canal with 2 LV papillary muscles, the interpapillary muscle angle is smaller than normal. Because papillary muscles are situated at the base of the valve commissures, the interpapillary muscle angle is an indicator of the size of the left lateral leaflet component (Fig. 4). Thus, the small interpapillary muscle angle in patients with complete common AV canal suggests that the left lateral leaflet is relatively small in such patients with 2 LV papillary muscles and is likely to be very poorly developed in those with complete common AV canal and solitary LV papillary muscle (interpapillary muscle angle, 0°).

Finally, although preoperative 2-D echocardiography appears to permit identification of LV papillary muscle anomalies in patients with complete common AV canal, the technique of intraoperative 2-D echocardiography promises to yield even better detail of the LV papillary muscle architecture.

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Journal: Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977; 39:1027–1034.

Chapter in Book: Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–139.

Book: Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:26.

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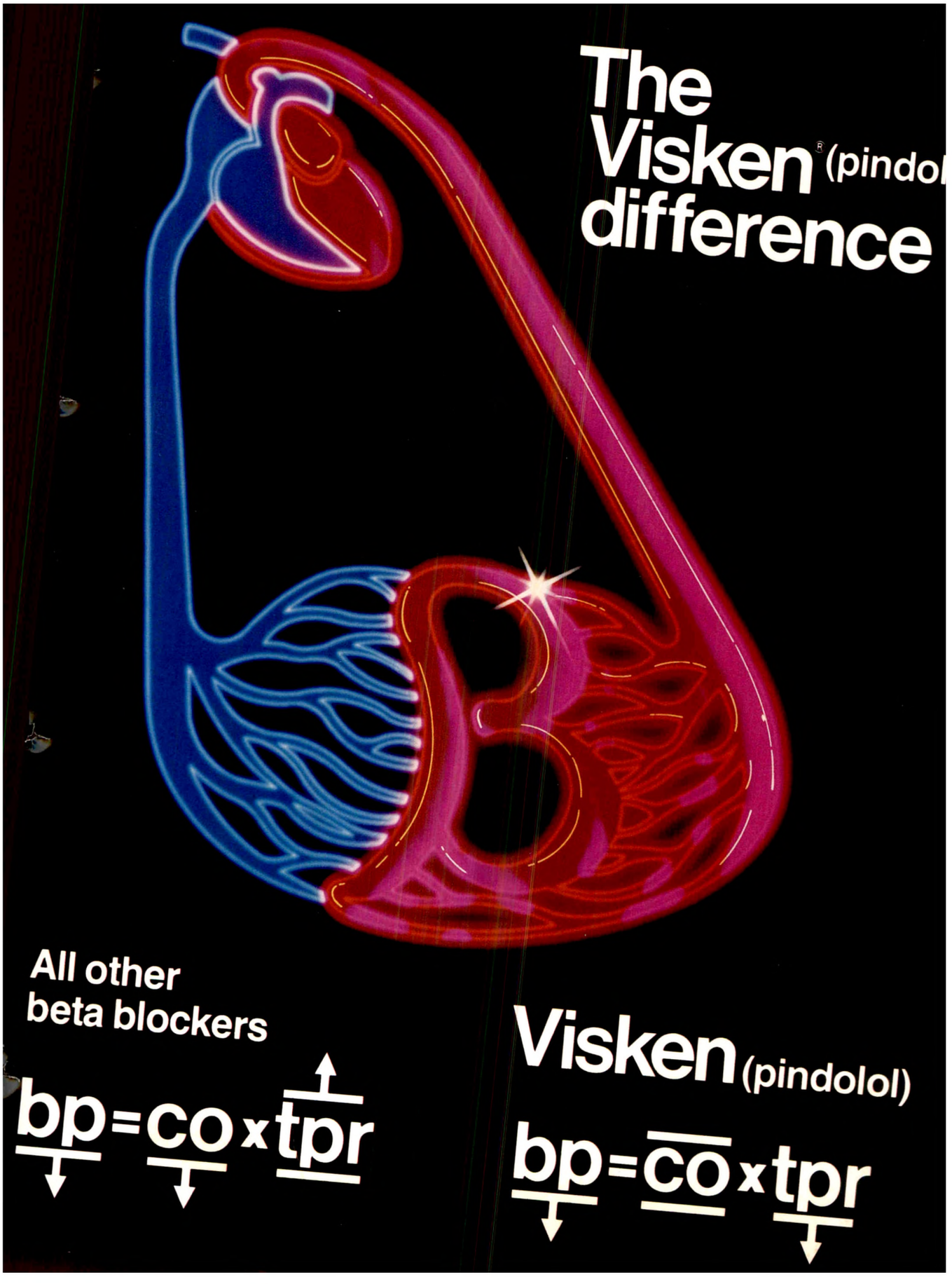
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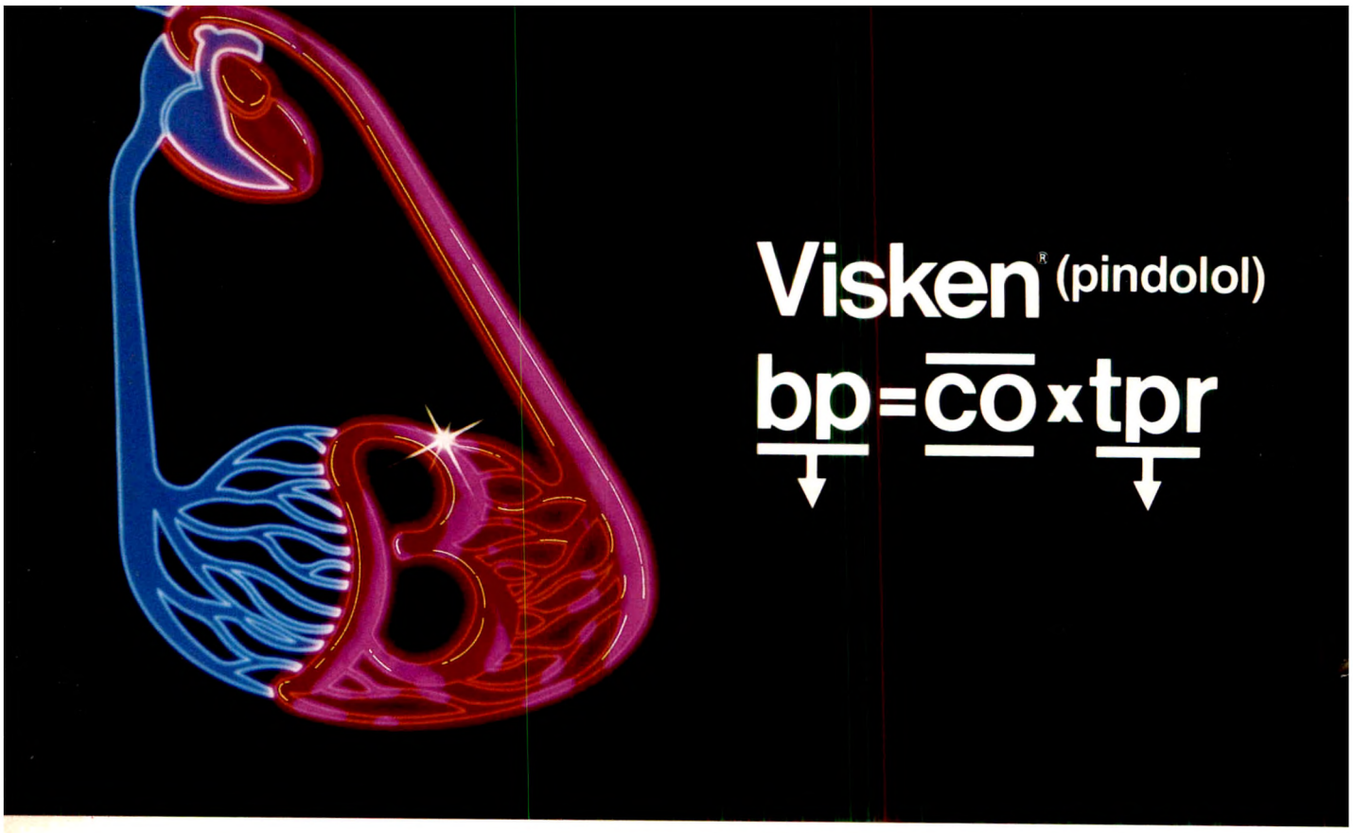

Makes hemodynamic sense in the treatment of hypertension

Reduces blood pressure

It's as effective as propranolol in normalizing blood pressure (dbp ≤ 90 mmHg) when used alone. It's also effective when used in combination with a diuretic.[1]

Has little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) maintains resting cardiac output during long-term therapy. The clinical significance of this has not been evaluated.

Reduces total peripheral resistance*

Visken (pindolol) reduces one of the recognized components of hypertension: increased peripheral resistance.* Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

Reduces exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

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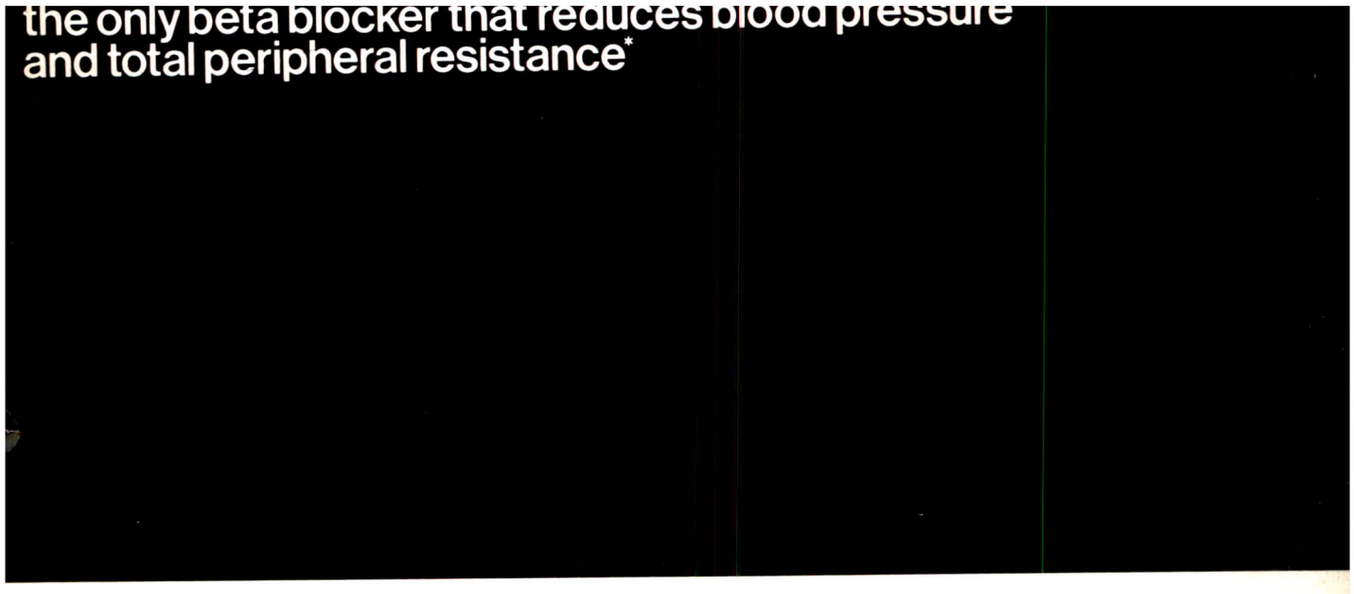
*The clinical significance has not been evaluated. See clinical significance statement on facing page of this advertisement.

the only beta blocker that reduces blood pressure and total peripheral resistance*



Has little effect on resting heart rate

Visken® (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute.

The clinical significance has not been evaluated

The clinical significance of maintaining resting cardiac output, resting heart rate and reduced total peripheral resistance has not been evaluated and there is no evidence or reason to believe that exercise cardiac output is less affected by Visken (pindolol) than other beta blockers.

Maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

Favorable side effect profile

Low incidence of bradycardia

Low incidence of cold extremities

Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

*See clinical significance statement.

References:
1. Data on file, Sandoz Pharmaceuticals.
2. Wilcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *J Cardiovasc Pharmacol* 3:598-611, 1981.

Please see next page of this advertisement for brief summary of prescribing information.

Visken® (pindolol)

Available in 5 mg and 10 mg tablets

Convenient bid dosage

Dosage should be titrated on an individual basis.
Many patients respond to 10-30 mg a day in divided doses.

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a beta$_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ⩾80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 10 mg b.i.d. alone or in combination with other antihypertensive agents. Many patients will respond to 15 mg per day (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactory reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 mg per day at 2-3 week intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05). [VIS-Z2 9/1/82]

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

Anatomic Obstruction of the Right Ventricular Outflow Tract In Transposition of the Great Arteries

RUDOLF J. MOENE, MD, ARENTJE OPPENHEIMER-DEKKER, MD, and MARGOT M. BARTELINGS, MD

In 126 hearts with transposition of the great arteries (TGA), morphologic features of the right ventricular (RV) outflow tract were analyzed. Distinct anatomic outflow tract obstruction was found in 15 of the 55 hearts with a ventricular septal defect (VSD) (27%): 12 had a perimembranous defect (predominantly extending into the infundibulum), 2 had an inlet, and 1 had an infundibular defect. In 12 hearts, outflow tract obstruction was caused by anterior displacement of infundibular septum and ventriculoinfundibular fold; in 3 hearts, it was caused by bulging of the trabecula septomarginalis or ventriculoinfundibular fold, or both. Of 71 hearts with an intact ventricular septum, only 2 (3%) had RV outflow tract obstruction: 1 had a trabecula in front of the aortic ostium and in the other an aberrant hypertrophic muscle bundle crossed the RV cavity, obstructing the entrance to the infundibulum. Associated malformations included aortic arch malformations (6 cases) and tricuspid valve anomalies (6 cases). Thus, anatomic RV outflow tract obstruction may constitute a complicating factor in TGA, notably in cases with VSD. A systemic RV blood pressure may trigger hypertrophy, resulting in progression of the obstruction; establishing normal RV pressure by a "switch" procedure might prevent this progression.

The left ventricular outflow tract in complete transposition of the great arteries (TGA) has received extensive attention in numerous studies; several investigators have outlined the anatomic features of left ventricular outflow tract obstruction.[1,2] In contrast, the right ventricular (RV) outflow tract has received little attention and anatomic RV outflow tract obstruction has rarely been described in TGA.[3,4] More recently, Freedom et al[5] and Schneeweiss et al[6] reported angiocardiographic and pressure data from patients with TGA and subaortic stenosis. This study determines the frequency of RV outflow tract obstruction in specimens with TGA and characterizes its morphologic features.

Methods

Case material: One hundred twenty-six hearts with situs solitus, atrioventricular concordance, and ventriculoarterial discordance were available from the collection of the Laboratory of Anatomy and Embryology at Leiden: 71 with intact ventricular septum and 55 with ventricular septal defect (VSD). In all cases the pulmonary trunk was mainly committed to the left ventricle, thus excluding forms of double outlet right ventricle in which the RV outflow tract already has been studied and described by several workers.[7,8] In most specimens, the aortic valve was anterior and to the right of the pulmonary valve; in some cases there was a side-by-side relationship. Excluded were complicated hearts with so-called "posterior transposition" and with straddling atrioventricular valves.

The specimens were studied with special attention focused on the presence or absence of anatomic indications of RV outflow tract obstruction; 15 normal hearts of different ages served as controls.

Definitions: The RV muscular structures are described according to the terminology proposed by Anderson et al.[9] These investigators used the term *crista supraventricularis* only in the description of hearts with normal RV outflow tracts, those without anomalies which derange the alignment of the outflow musculature. It should be noted that some other workers, among them Schneeweiss et al,[6] do use the same term in hearts with outflow tract abnormalities. We agree with Anderson et al[9] that in hearts with outflow tract anomalies 3 separate structures warrant description: the infundibular septum, the ventriculoinfundibular fold (together constituting the crista supraventricularis in the normal heart), and the trabecula septomarginalis. The VSDs are described and classified according to the classification by Soto et al.[10] In the scope of the present study, we used in addition the term *displacement of the infundibular septum* because it emphasizes the morphologic features more adequately than the general term *malalignment* (this term does not figure into Soto's classification).

Results

The normal subaortic infundibular anatomy in TGA is depicted in Figure 1. Anatomic evidence of RV outflow tract obstruction was identified in 15 of the 55

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Address for reprints: Rudolf J. Moene, MD, Department of Paediatric Cardiology, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

hearts with VSD (27%) and in 2 of the 71 hearts with intact ventricular septum (3%). The 17 patients ranged in age from 1 day to 4.5 years (median 9.5 months). Of the 15 hearts with VSD, 12 had a perimembranous defect with predominant extension into the infundibulum, 2 had a muscular inlet defect, and 1 had a muscular infundibular defect. Among the 17 hearts with RV outflow tract obstruction, various outflow tract malformations were found which could be classified into 2 categories: (1) anterior displacement of the infundibular septum and ventriculoinfundibular fold, and (2) redundant muscle tissue.

Anterior displacement of the infundibular septum and ventriculoinfundibular fold (12 cases) was associated with 2 morphologic features (Fig. 2). First, it results in distance reduction between these structures on the one hand and the anterior RV wall on the other hand and thus in outflow tract narrowing. Second, it results in subpulmonary localization of the (perimembranous) VSD. The infundibular septum, merging with the trabecula septomarginalis, formed the anterior edge of the roof of the defect. The anteroinferior rim of the defect was formed by the trabecula septomarginalis. As viewed from the left ventricle, the posterior margin of the defect was the mitral-pulmonary fibrous continuity. Dual insertion of the medial papillary muscle was present in 7 cases with anterior displacement of the infundibular septum and ventriculoinfundibular fold, resulting in embracement of the subpulmonary VSD by 2 chordal groups: 1 group inserting into the trabecula septomarginalis, and the second chordal group inserting into the infundibular septum (Fig. 3).

Anatomic obstruction of the RV outflow tract by redundant muscle tissue was found in 5 cases. Three cases demonstrated bulging of the trabecula septomarginalis or ventriculoinfundibular fold, or both (Fig. 4); in 1 case, a trabecula was located ventral to the aortic ostium (Fig. 5) and in another case an aberrant hypertrophic muscle bundle crossed the RV cavity and obstructed the entrance to the outflow tract (Fig. 6). Associated malformations included aortic arch anomalies in 6 (35%) of the 17 hearts with RV outflow tract obstruction: isthmus hypoplasia in 3, local coarctation in 2, and interruption in 1.

In addition, the following anomalies of the tricuspid valve apparatus were identified: 2 hypoplastic valves (Fig. 7), 1 dysplastic valve, and 3 cases in which some chordae of the anterior tricuspid valve leaflet were connected to an accessory papillary muscle arising from the parietal wall of the right ventricle (Fig. 4). One mitral valve showed a parachute deformity. The aortic and pulmonary valves were normal in all 17 cases. Catheterization data were available from 4 patients. In 3 cases with a perimembranous subpulmonary VSD, the catheter was advanced from the right ventricle to the pulmonary artery; however, efforts to enter the as-

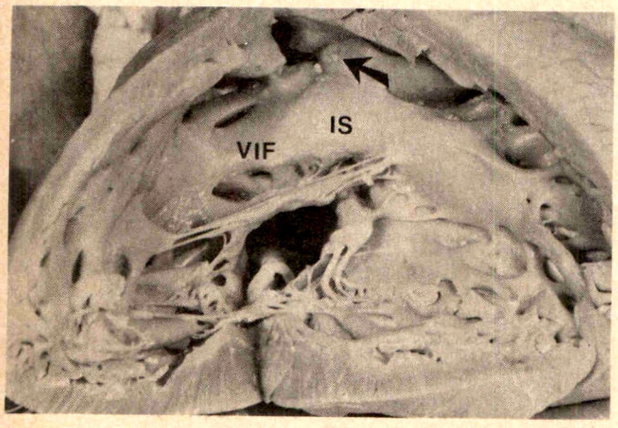

FIGURE 1. Normal subaortic infundibular anatomy in TGA. The **arrow** points to the aortic orifice with 3 normal semilunar cusps. IS = infundibular septum; VIF = ventriculoinfundibular fold.

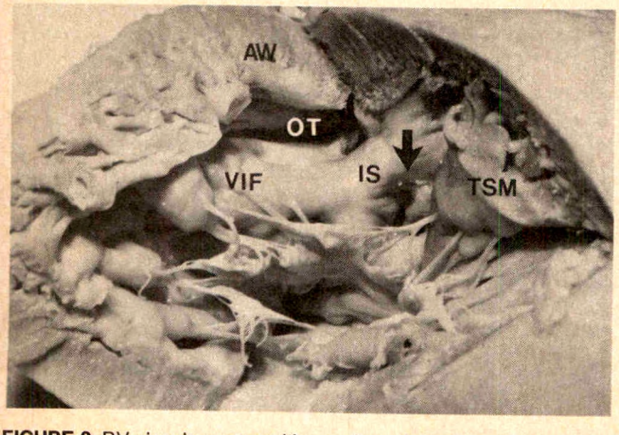

FIGURE 2. RV view in a case with a perimembranous, subpulmonary VSD (**arrow**) predominantly extending into the infundibular septum (IS). The infundibular septum and ventriculoinfundibular fold (VIF) are displaced anteriorly, thus narrowing the outflow tract (OT). AW = anterior wall of the right ventricle; TSM = trabecula septomarginalis.

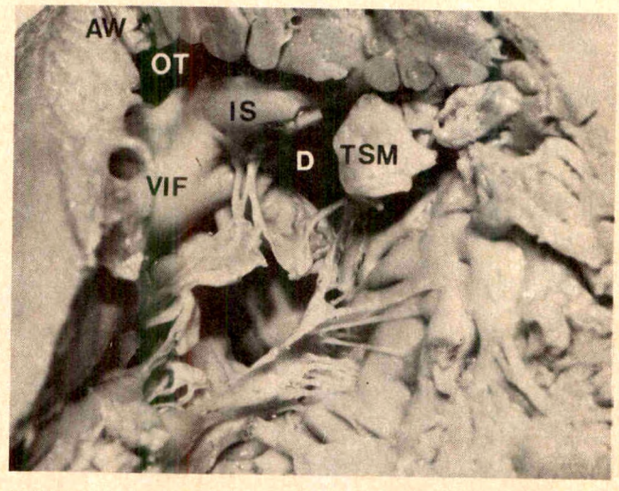

FIGURE 3. Conspicuous narrowing of the RV outflow tract (OT) by anterior displacement of the infundibular septum (IS) and ventriculoinfundibular fold (VIF). Dual insertion of the medial papillary muscle results in embracement of the perimembranous subpulmonary defect (D) by 1 chordal group inserting into the infundibular septum and another one inserting into the trabecula septomarginalis (TSM). AW = anterior wall of the right ventricle.

cending aorta from the right ventricle remained unsuccessful.

A pressure gradient of 30 mm Hg across the aortic outflow tract was diagnosed in the case with a bulging ventriculoinfundibular fold. In the hearts without RV outflow tract obstruction, hypertrophy of the ventriculoinfundibular fold, the infundibular septum, and the trabecula septomarginalis, separately or in combination, was noted in 20 specimens with a VSD and 17 specimens with an intact ventricular septum. One of those cases, with a hypertrophic ventriculoinfundibular fold, is shown in Figure 8.

Discussion

Data from the literature concerning the RV outflow tract in TGA are scarce and contradictory. Becu and Gallo[11] found abnormal muscular bands in the outflow tract of all their 67 studied hearts; this anatomic distortion was so marked in many instances that "the morphology of the subaortic chamber only superficially

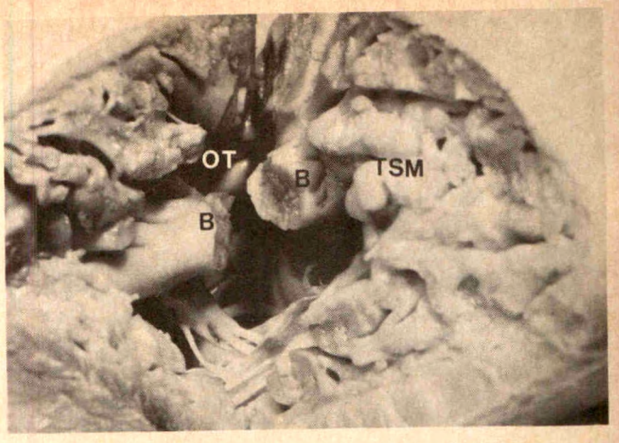

FIGURE 6. Cut aberrant hypertrophic muscle bundle (B) crossing the RV cavity and obstructing the entrance to the outflow tract (OT). TSM = trabecula septomarginalis.

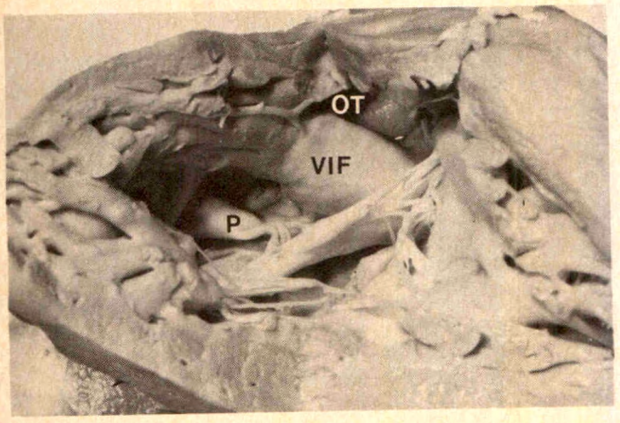

FIGURE 4. Narrowing of the RV outflow tract (OT) by a hypertrophic ventriculoinfundibular fold (VIF). Note the accessory tricuspid papillary muscle (P); the presence of a small inlet VSD is not visible in this view.

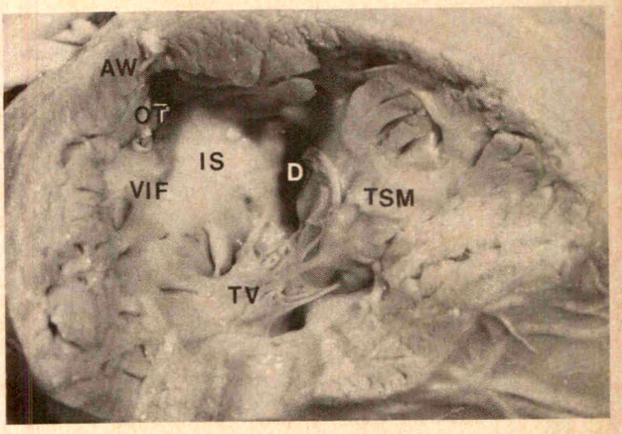

FIGURE 7. Narrowing of the RV outflow tract (OT) by anterior displacement of the hypertrophic infundibular septum (IS) and ventriculoinfundibular fold (VIF); the VSD (D) is perimembranous and subpulmonary. Note hypoplasia of the tricuspid valve (TV). AW = anterior wall of the right ventricle; TSM = trabecula septomarginalis.

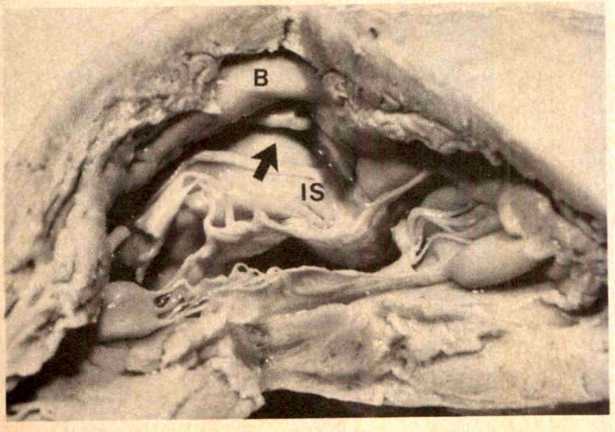

FIGURE 5. Narrowing of the outflow tract (**arrow**) by an aberrant hypertrophic muscle bundle (B) in front of the aortic ostium. IS = infundibular septum.

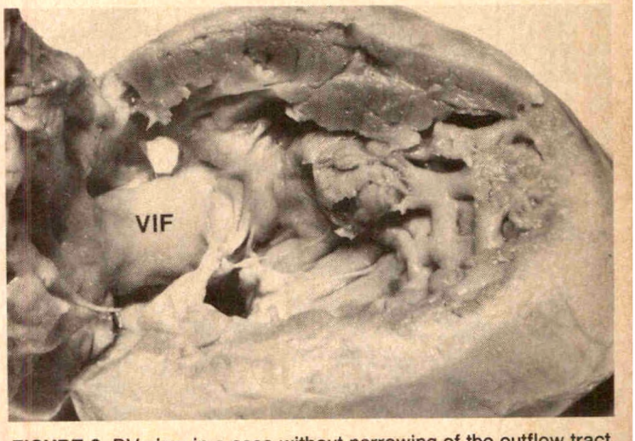

FIGURE 8. RV view in a case without narrowing of the outflow tract. Apart from the generalized hypertrophy, there is conspicuous bulging of the ventriculoinfundibular fold (VIF).

resembled a normal right ventricle." In contrast with those findings, Anderson and Becker,[12] in a recent review of the morphologic features of TGA, do not mention abnormal muscular bands. In their view, infundibular pathology is restricted to abnormal orientation of the infundibular septum in cases with intact ventricular septum, and to malalignment of the infundibular septum in case of an infundibular VSD. Malalignment (termed *displacement* by us) of the infundibular septum was also identified in the present material. However, in addition, our observations point to the presence of an abnormal, hypertrophic ventriculoinfundibular fold, infundibular septum, trabecula septomarginalis, or a combination of these in a considerable number of cases; this hypertrophy often exceeds the hypertrophy of the free wall of the right ventricle which is always present in cases with TGA.[13] Although the present observations are estimations since no quantitative methods are available to characterize size, shape, and alignment of the aforementioned structures, the differences from "normal" are distinct.

According to the literature, anatomic obstruction of the RV outflow tract in TGA seems to be rare. Elliott et al[3] found in 4 of 38 cases with intact ventricular septum slight obstruction of the subaortic area resulting from moderate enlargement of the crista supraventricularis, and in 3 of 22 cases with a VSD, stenosis of the subaortic area by a hypertrophied crista supraventricularis. Shaher[4] described a similar case and quotes another 2 cases from other studies. Clinical data concerning 5 patients with subaortic stenosis were reported by Schneeweiss et al[6]; in those patients, 4 of whom had a VSD and 2 a coarctation of the aorta, the stenosis was demonstrated by a pressure gradient of 30 to 55 mm Hg and by angiocardiography. In their control group of 67 patients without subaortic stenosis, various degrees of hypertrophy of what they termed *the crista supraventricularis* were identified by the angiocardiogram. Their findings suggest the presence of a sliding scale from minor to major pathology of the crista supraventricularis, which corresponds with the results of the present study, if we translate crista supraventricularis as ventriculoinfundibular fold and infundibular septum. Unfortunately, Schneeweiss et al[6] did not classify the VSDs in their patients. In 12 of our cases, a VSD was accompanied by anterior displacement of the infundibular septum and ventriculoinfundibular fold resulting in subpulmonary localization of the defect. This type of defect has been described as subpulmonary defect with overriding pulmonary trunk and malalignment of the infundibular septum by Huhta et al[14] in the scope of a study on tricuspid valve abnormalities in TGA.

Apart from tricuspid valve abnormalities, which were also present in 4 of our cases with this type of defect, the investigators refer to subaortic obstruction by a malaligned hypertrophic infundibular septum. Given the lack of sufficient pressure data to demonstrate the flow-obstructive character of the lesions observed, we are left with possible supportive evidence. In this respect, the incidence of 6 aortic arch malformations in the underlying 17 specimens is of importance, since the genesis of arch anomalies generally has been accepted as being the consequence of intracardiac obstructive factors. Having demonstrated anatomic obstruction of the RV outflow tract in hearts with subpulmonary VSD and anterior displacement of the infundibular septum, a similar problem may be expected in other anomalies with displacement of the infundibular septum to the right, as in the double outlet right ventricle with subpulmonary VSD. This is confirmed by several workers who established the close relationship between this malformation and subaortic stenosis.[7,8]

Together with data from the literature, the present study indicates that anatomic obstruction of the RV outflow tract in TGA does exist, and that it is usually characterized by anterior displacement of the infundibular septum and ventriculoinfundibular fold (in association with a perimembranous defect) or, in a minority of the cases, by redundant muscle tissue. More studies concerning the relation between anatomy and clinical data are needed to establish the functional implications and natural history of these anomalies. One practical consequence is mentioned by Huhta et al,[14] who pointed out that hypertrophy of a malaligned infundibular septum can add difficulty to the surgical creation of an unobstructed left ventricular outflow tract in case of a Rastelli approach. Next, it seems important to realize that a systemic RV blood pressure may trigger hypertrophy resulting in progression of the obstruction; one could speculate that normalization of the RV pressure by performing a switch procedure may prevent this progession.

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Quantitative Angiographic and Morphologic Aspects of Aortic Valve Atresia

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Quantitative angiographic measurements were performed in 15 infants aged 1 to 35 days who had aortic valve atresia with intact ventricular septum and hypoplastic left ventricle. Thirteen infants had similar measurements performed at autopsy. The latter measurements were smaller than those found at angiography (because of shrinkage), but their relationship was predictable. Angiographic right ventricular (RV) volumes were 2 and 4 times normal in diastole and systole, respectively. The RV volume measured at autopsy was >3 times normal. Mean RV ejection fraction was 0.40; it was below normal in 10 infants. Maximal right atrial volume was >2 times normal, and mean left atrial maximal volume was two-thirds normal. The relation between circumferences of the aortic arch and ascending and descending aorta was similar at angiography and autopsy.

Aortic valve atresia (AVA) is the most malignant form of congenital heart disease.[1] Because of rapid clinical deterioration, infants with this lesion often are not extensively investigated. This study reports detailed angiographic measurements in infants with AVA with an intact ventricular septum and compares these with related autopsy measurements.

Methods

We studied 15 infants (12 male and 3 female) aged 1 to 35 days, all of whom had cardiac catheterization with biplane selective angiocardiography. The diagnosis was confirmed at autopsy in all infants.[2] Table I shows the clinical data. Birth weight was 2.8 to 4.1 kg. Symptoms appeared at 1 to 35 days of age. Eleven infants became ill in the first week of life, and 12 died within 3 days of the onset of symptoms. One became symptomatic at 19 days and lived 48 days after palliative surgery.[3] Eight infants had mitral valve atresia, and the remaining 7 had mitral stenosis. None had a ventricular septal defect, and the left ventricle was minute in all.

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Cardiac volume and dimension was determined from biplane cineangiocardiograms as described previously.[4–6] Right ventricular (RV) and right atrial volume was calculated by Simpson's Rule and was corrected by regression equations obtained from plastic casts of the heart chambers.[4–6]

The following were measured at angiography: RV end-diastolic and end-systolic volume, stroke index, ejection fraction, and maximal right and left atrial volume; diameter of the ascending aorta (1 cm above the atretic aortic valve), aortic arch (proximal to the origin of the left subclavian artery), descending aorta (just distal to the ductus arteriosus), RV inflow and outflow tracts, and pulmonary and tricuspid valves, all measured in the lateral view. Spatial RV inflow (tricuspid valve to apex) and outflow (pulmonary valve to apex) tract lengths were calculated using the formula $\sqrt{x^2 + y^2 + z^2}$ from coordinates measured in the anteroposterior and lateral views. Normal values were obtained from our own laboratory and from Nakazawa et al[7] and Graham et al.[8–10]

Autopsy analysis was based on standard fixation by controlled pressure coronary perfusion as described elsewhere.[11,12] The following parameters were measured: heart weight; diameter of the tricuspid and pulmonary valves, ascending aorta (1 cm above the atretic valve), transverse arch (proximal to the origin of the left subclavian artery), and descending aorta (distal to the ductus arteriosus); RV inflow (tricuspid anulus to apex) and outflow (pulmonary anulus to apex) tract length; inflow (moderator band to base of anterior papillary muscle along free wall) and outflow (greater perimeter) diameter; and RV volume.[11,12]

TABLE I Clinical and Laboratory Findings

Case	Sex	Age at Study (days)	Age at Death (days)	Weight at Study (kg)	Arterial Blood Gases		Angiocardiography				Autopsy	
					pH	PaO_2	Stroke Index (ml/m²)	Ejection Fraction	Maximal Atrial Volumes (ml) Right	Maximal Atrial Volumes (ml) Left	Heart Weight (g)	Mitral Valve Atresia
1	F	4	4	3.40	7.27	53	40	0.50	13	2.6	30	0
2	M	1	3	3.40	7.0	35	50	0.42	20	1.5	32	+
3	M	5	5	3.63	7.25	65	20	0.21	20	2.4	34	0
4	F	2	3	4.10	7.05	76	23	0.29	9	...	26	+
5	M	1	1	2.80	7.30	56	37	0.40	...	2.5	...	+
6	M	19	67	3.00	7.33	24	35	0.45	11	5.7	50	0
7	M	39	41	3.20	7.39	26	50	0.56	...	5.5	51	+
8	M	14	15	3.50	7.30	49	45	0.39	17	1.6	54	0
9	M	19	22	3.60	7.22	19	26	0.39	16	3.4	51	0
10	M	7	7	3.70	7.28	66	50	0.53	18	2.4	50	+
11	M	2	3	3.01	7.38	43	36	0.54	14	2.9	33	0
12	F	5	5	2.40	7.22	34	20	0.30	...	3.3	32	+
13	M	2	2	3.60	7.30	70	25	0.23	...	...	26	0
14	M	1	3	3.06	7.27	75	25	0.19	20	3.7	...	+
15	M	2	2	3.12	7.20	35	41	0.57	19	3.4	...	+
Mean ± SD	...	...	...	...	...	...	35 ± 11	0.40 ± 0.13	16 ± 4	3.1 ± 1.3	39 ± 11	...
Normal mean ± SD	...	...	...	...	...	...	35 ± 7	0.61 ± 0.10	10 ± 5	7.5 ± 2.6	21 ± 5	

PaO_2 = partial arterial oxygen pressure; SD = standard deviation.

Results

Autopsy findings (Tables I and II): These measurements were performed for comparison with the angiographic measurements.

Angiographic findings (Tables I and II): The right ventricle was dilated, was heavily trabeculated, and had reduced wall motion. RV end-diastolic and end-systolic volumes were 2 and 3 times normal, respectively, whereas the stroke index was near normal. RV ejection fraction was below normal in two thirds of the cases. Except for the length of the outflow and the diameter of the inflow tract, RV dimensions were significantly larger in patients with AVA than in normal control subjects. The left ventricle was usually not visualized. Maximal right and left atrial volume was more than twice and two-thirds normal, respectively. Both atria contracted forcefully. In Case 6, the interatrial communication became markedly restrictive during a 1-month period of observation.[3]

Comparison of angiographic and autopsy measurements: The dimensions of the various cardiac structures were consistently greater at angiography because of shrinkage of the autopsy specimens. When the latter was taken into account, angiographic measurements could be predicted with good accuracy from autopsy measurements.[5,6] The diameter of the RV outflow tract was an exception: angiographic and autopsy dimensions were similar. The mean RV volume measured at autopsy was smaller than the angiographic end-systolic volume. There was no significant difference between the RV inflow and outflow tract lengths measured by angiography or at autopsy. The tricuspid valve diameter measured at angiography was 1.6 times larger than that at autopsy, and the pulmonary valve 1.3 times larger. The ratio between the main pulmonary artery and descending aorta circumference was 1.9 on angiography and 1.8 at autopsy, respectively. At angiography, the mean ascending aortic circumference was 0.4 and that of the aortic arch 0.7 times that of the descending aorta. Autopsy measurements showed a similar relation, the ratios being 0.4 and 0.6, respectively.

Discussion

The only published angiographic measurements in AVA are those of Farooki et al,[13] who found an average of 0.38 ± 0.05 cm for the aortic root (range 0.29 to 0.44, n = 7) and 0.27 ± 0.05 cm for the ascending aorta (range 0.22 to 0.35, n = 7). The former measurements, made at the aortic sinuses, are not comparable with those of the present study. However, the size of the ascending aorta is virtually identical to the present data.

Infants with AVA and intact ventricular septum have a functional single right ventricle, subject to volume and pressure overload, resulting in extreme RV dilatation and significant hypertrophy in the newborn period. The present study confirms that most angiographic and pathologic measurements related to the right-sided cardiac structures are larger in patients with AVA compared with normal subjects.[11,12] Although the autopsy measurements are smaller than the angiographic measurements because of shrinkage, the latter can be predicted fairly accurately from the former. The ratios observed angiographically and at autopsy between the dimensions of the ascending aorta, aortic arch, and descending aorta are similar.

Pathologic studies suggest that longer term survivors with AVA and intact ventricular septum have a thicker left atrial wall, indicating progressive obstruction at the site of the foramen ovale.[2] Prolonged retention of angiographic contrast material in the left atrium corro-

TABLE II Angiographic and Autopsy Measurements

	Right Ventricle														Aorta					
	Volumes (ml)			Spatial Length (cm)				Ventricular Diameters (cm)				Valve Diameters (cm)				Aortic Diameters (cm)					
	Angio			Angio		Aut		Angio		Aut		Tricuspid		Pulmonary		Angio			Aut		
Case	EDV	ESV	Aut	RV_i	RV_o	RV_i	RV_o	RV_i	RV_o	RV_i	RV_o	Angio	Aut	Angio	Aut	Asc	Arch	Desc	Asc	Arch	Desc
1	18	9	9	5.0	4.7	3.3	3.6	3.4	1.2	1.3	1.5	2.1	1.6	1.3	1.1	0.2	0.4	0.7	0.1	0.4	0.5
2	26	15	8	4.9	5.3	3.0	3.6	3.5	1.7	1.3	1.4	2.5	1.4	1.3	1.0	0.3	0.4	0.8	0.3	0.4	1.0
3	23	18	9	5.5	5.4	4.2	3.5	3.6	2.2	1.3	1.6	2.8	1.4	1.6	1.3	0.3	0.6	0.8	. . .	. . .	. . .
4	20	14	6	5.8	5.2	2.8	3.1	3.5	1.8	1.0	1.2	2.7	1.6	1.4	0.9	0.3	0.5	0.8	0.2	0.4	0.6
5	18	11	7	4.5	4.5	3.0	3.4	3.0	1.3	1.1	1.3	2.3	1.6	1.4	1.0	0.2	0.4	0.8	0.1	0.4	0.5
6	17	10	11	4.8	4.8	3.0	5.2	2.7	1.7	1.8	1.4	2.7	1.6	1.5	0.8	0.2	0.6	0.8	0.3	0.4	0.6
7	20	9	8	4.7	4.6	3.6	3.2	2.8	1.3	1.3	1.5	2.5	1.8	1.3	1.4	0.3	0.6	0.8	0.2	0.4	0.6
8	25	15	16	5.2	5.0	3.8	4.0	3.5	1.8	1.4	2.1	2.3	1.8	1.4	1.3	0.3	0.4	0.6	0.2	0.4	0.6
9	13	18	14	4.0	4.2	4.3	4.3	3.2	1.9	1.8	1.9	2.1	1.5	1.4	1.0	0.5	0.5	0.7	0.4	0.4	0.7
10	23	11	11	6.1	4.8	3.5	4.0	3.7	1.6	1.3	1.8	2.7	1.6	1.6	1.3	0.3	0.6	0.9	0.2	0.4	0.6
11	13	6	9	4.8	4.6	3.2	3.6	2.5	1.8	1.1	1.5	2.1	1.7	1.6	1.4	0.3	0.6	0.8	0.2	0.5	1.4
12	12	8	9	4.4	4.0	3.7	3.8	2.4	1.4	1.4	1.5	2.0	1.6	1.3	1.2	0.2	0.4	0.5	0.4	0.5	1.2
13	25	19	9	5.7	5.0	3.5	4.0	3.5	2.0	1.1	1.5	2.3	1.3	1.4	1.1	0.2	. . .	0.9	0.4	0.5	0.7
14	27	22	. . .	5.6	5.1	. . .	. . .	3.6	1.8	. . .	. . .	2.9	. . .	1.6	. . .	0.3	0.5	1.0	. . .	. . .	. . .
15	14	6	. . .	4.1	4.1	. . .	. . .	2.4	1.2	. . .	. . .	2.0	. . .	1.5	. . .	0.3	0.3	0.7	. . .	. . .	. . .
Mean ± SD	20 ± 5	13 ± 5	10 ± 3	5.0 ± 0.6	4.8 ± 0.4	3.5 ± 0.5	3.8 ± 0.5	3.2 ± 0.5	1.6 ± 0.3	1.3 ± 0.3	1.6 ± 0.3	2.4 ± 0.3	1.5 ± 0.2	1.4 ± 0.1	1.1 ± 0.1	0.3 ± 0.1	0.1 ± 0.1	0.8 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.8 ± 0.3
NM ± SD	11 ± 5	4 ± 2	3 ± 1	4.3 ± 0.7	4.7 ± 0.8	2.9 ± 1.0	3.0 ± 0.3	3.1 ± 0.5	1.2 ± 0.2	1.1 ± 0.2	1.0 ± 0.3	1.8 ± 0.3	1.1 ± 0.2	1.2 ± 0.1	0.7 ± 0.1	1.1 ± 0.1	. . .	0.7 ± 0.1	. . .	. . .	. . .

Angio = angiocardiography; Arch = aortic arch; Asc = ascending; Aut = autopsy; Desc = descending; EDV = end-diastolic volume; ESV = end-systolic volume; NM = normal mean; RV_i = right ventricle inflow tract; RV_o = right ventricle outflow tract; SD = standard deviation.

borates this finding. In Case 8 in the present series angiographic studies were performed at 19 days and again after palliative surgery, at 48 days of age.[3] A reduction in the size of the foramen ovale resulting in severe left atrial obstruction was confirmed at autopsy.

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Increased Left Ventricular Ejection Fraction After a Meal: Potential Source of Error in Performance of Radionuclide Angiography

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The effect of a standardized meal on left ventricular (LV) ejection fraction (EF) was determined by equilibrium radionuclide angiography in 16 patients with stable congestive heart failure but without pulmonary or valvular heart disease. LVEF was determined in the fasting state and 15, 30, and 45 minutes after a meal. Patients with moderately depressed fasting LVEF (30 to 50%), Group I, had a mean increase of 6.9 ± 2.9% ($p < 0.005$) in the LVEF at 45 minutes after the meal. Patients with severely depressed fasting LVEF (<30%), Group II, had no change after the meal. It is concluded that significant increases in LVEF may occur after meals in patients with moderate but not severe left ventricular dysfunction. Equilibrium radionuclide angiography studies that are not standardized for patients' mealtimes may introduce an important unmeasured variable that will affect the validity of data in serial studies of left ventricular function.

Postprandial increase in cardiac output is a well-recognized phenomenon in animals, but little is known about the effects of eating on cardiac performance in man. More specifically, no data are available to assess changes produced by eating on routinely measured indexes of ventricular function. The left ventricular (LV) ejection fraction (EF) is one of the most commonly used variables in assessing ventricular function. EF measurements by equilibrium radionuclide angiography have been shown to correlate well with values obtained by invasive left ventriculography and to be highly reproducible, with variations of <2.0 ± 2.1% in serial patient examinations.[1] This study determines the effect of a standardized meal on the resting LVEF in a group of patients with stable congestive heart failure.

From the Nuclear Medicine Service, and the Cardiology Service, Department of Medicine, Letterman Army Medical Center, Presidio of San Francisco, California, and the Department of Medicine, University of California, San Francisco. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. Manuscript received July 20, 1982; revised manuscript received March 10, 1983, accepted March 12, 1983.

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Methods

The study group comprised 16 patients (14 men, 2 women), aged 29 to 78 years. All patients were normotensive. Thirteen had stable congestive heart failure secondary to atherosclerotic coronary heart disease, and 3 had idiopathic dilated cardiomyopathy. The patients were divided into 2 groups: Group I, patients with mild to moderately depressed resting EF (30 to 50%); and Group II, patients with severely depressed resting EF (<30%). No patient had a recent cardiac event or change in symptoms, therapeutic requirements, or functional class (New York Heart Association) within 6 weeks of the study. Patients with pulmonary or valvular heart disease were excluded from the study.

All patients were studied in the resting, supine state after fasting for 6 to 12 hours before examination, and all medications were withheld for at least 6 hours before testing. Red blood cells were labeled in vivo by an injection of 25 mCi (9.5×10^8 Bq) of technetium-99m pertechnetate preceded by an intravenous injection of stannous ion (2 mg). Patients underwent electrocardiographic gated equilibrium radionuclide left ventriculography before eating and at 15, 30, and 45 minutes after eating a standardized hospital breakfast composed of approximately 50% carbohydrate, 30% fat, and 20% protein and totalling 700 to 900 calories. No hot or iced liquids, coffee, or tea were included in the meal. Data acquisition was performed in a modified left anterior oblique projection by a gamma camera equipped with a general purpose collimator

TABLE I Comparison of Fasting and Postprandial Ejection Fractions

Group	Patients (n)	Ejection Fractions (%)					
			Postprandial				
		Fasting	15 Minutes	30 Minutes	45 Minutes	Change	p Value
I	10	37.7 ± 7.0	40.2 ± 7.0	43.1 ± 7.7	44.6 ± 7.3	6.9 ± 2.9	<0.005
II	6	23.6 ± 4.4	24.0 ± 4.7	23.6 ± 4.5	24.8 ± 5.0	1.2 ± 1.8	>0.10 (NS)

All values are means ± standard deviation.
NS = not significant.

(Picker Dynamo, South San Francisco, California) interfaced with a dedicated minicomputer (Medical Data Systems A^2, Ann Arbor, Michigan). All patients were in sinus rhythm. Heart rate and supine brachial arterial blood pressure were recorded. Stored data were processed by semiautomated computer system software using varying regions of interest for EF determinations. Statistical analysis was performed using analysis of variance with repeated measures.

Results

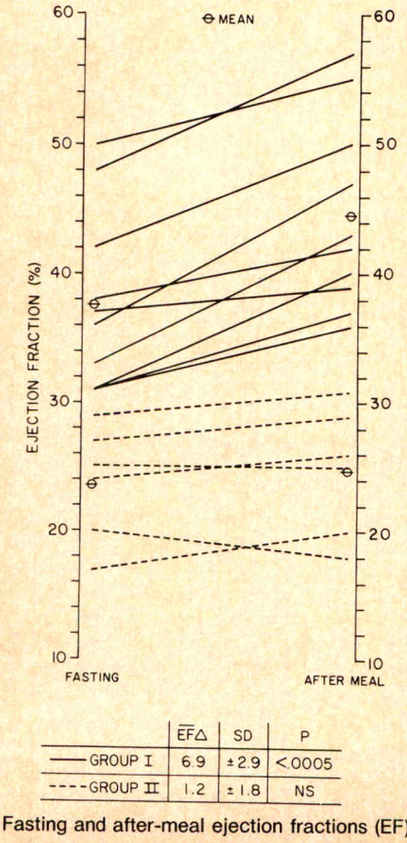
Analysis of the data revealed that the response to eating differed markedly between the 2 groups (Table I). Patients in Group I had an increase in average EF from 38% fasting to 45% at 45 minutes after eating. No Group I patient had an EF lower than the baseline fasting value during the performance of the test (Fig. 1). The mean increase in EF (6.9 ± 2.9%) was significant (p <0.005) (Fig. 2). The largest individual increase in this group was seen in Patient 3, whose EF increased 11% (from 36% to 47%), and the smallest incremental changes in EF occurred in Patients 7 and 8 (increases of only 2% and 3%, respectively). These 2 patients had had an acute myocardial infarction approximately 8 weeks before study.

Patients in Group II had no statistically significant change in EF after eating, with a mean fasting EF of 24% and a mean EF after eating of 25%.

There were no significant changes in blood pressure or blood pulse after eating in either group, and no patient had angina pectoris during study.

Discussion

More than 50 years ago, Grollman[2] reported that cardiac output increases in response to feeding. Subsequent studies confirmed an increase in cardiac output, pulse rate, and generalized organ blood flow in the



	$\overline{EF\Delta}$	SD	P
GROUP I	6.9	±2.9	<.0005
GROUP II	1.2	±1.8	NS

FIGURE 1. Fasting and after-meal ejection fractions (EF). NS = not significant.

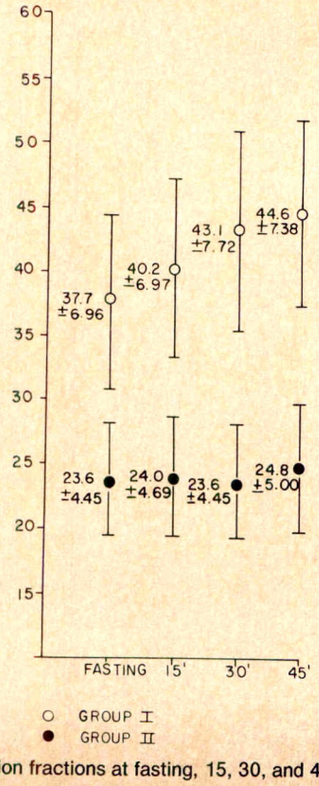


FIGURE 2. Ejection fractions at fasting, 15, 30, and 45 minutes.

postprandial state.[3,4] Further detailed observations in nonanesthetized animals have shown only a transient increase in cardiac output, pulse rate, and arterial blood pressure after eating,[5–7] with prolonged selective increases in mesenteric blood flow due to local vasodilation.[7] The cardiovascular effects of eating and digestion in man have rarely been subjected to investigation, either in the healthy person or in the presence of cardiac disease.[8,9]

Our study of patients who have stable congestive heart failure shows definite augmentation of LVEF after a meal in patients with moderate but not severe LV dysfunction. The mechanism by which this occurs may be a decrease in systemic vascular resistance as described in animal studies, resulting in LV unloading. In patients with more severe LV dysfunction, it can be speculated that chronically increased sympathetic nervous system tone may result in blunting or even preventing of the usual physiologic responses to a meal, or that these patients are less sensitive to the mild degree of afterload reduction induced by food intake because of continued high preload conditions.

Gated blood pool radionuclide angiography has gained widespread acceptance as a tool for assessing LV function. Ideally suited for serial longitudinal studies, it is both safe and noninvasive, with good reproducibility. However, to ensure the reproducibility of the test, factors that affect cardiac performance must be standardized for each examination. Our study demonstrates that significant increases in EF after eating exceed the accepted limits of EF variability utilizing radionuclide ventriculography.[1]

Thus, studies of cardiac performance that do not control mealtimes may introduce an important unmeasured variable. This uncontrolled variable may particularly affect the validity of data in serial comparative studies carried out at different hours of the day over several days, weeks, or months.

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Diagnostic Accuracy of Indium-111 Platelet Scintigraphy In Identifying Left Ventricular Thrombi

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This study defines the optimum imaging time window after injection of labeled platelet suspension for detection of left ventricular (LV) thrombi, identifies the most useful imaging views, and determines the reproducibility of this technique. A total of 662 images obtained from 64 patients were analyzed retrospectively on 2 separate occasions by 3 observers blinded as to patient identity, view (right anterior oblique, anterior, left anterior oblique, and left lateral), and time after injection of the platelet suspension that the images were obtained (0 to 2, 3 to 4, and 5 to 6 days). Images were categorized as either positive or negative. In every case surgical or autopsy verification of the presence or absence of LV thrombus was possible. The best combination of sensitivity, specificity, and diagnostic accuracy was found in the 3- to 4-day period in the left anterior oblique view and was 54 ± 5% (mean ± standard deviation), 98 ± 1%, and 85 ± 2%, respectively. Sensitivity, specificity, and diagnostic accuracy were not enhanced by adding additional views (right anterior oblique, left lateral, and anterior) to the left anterior oblique view in the 3- to 4-day time period. However, using multiple views, localization of thrombi to the left ventricle was facilitated. In a second retrospective analysis, a comparison of day 0 with day 3 to 4 images enhanced sensitivity and accuracy to 65 ($p < 0.001$) and 90% (not significant), respectively. Specificity was unchanged at 99%. Mean intra- and interobserver agreement was 91 and 88%, respectively. Thus, (1) indium-111 platelet scintigraphy is a reproducible and specific technique for identifying LV thrombus, and (2) we advise imaging on day 0 and again 3 to 4 days after injection of the platelet suspension in right anterior oblique, left anterior oblique, left lateral, and anterior views to maximize accuracy and to facilitate localization of LV thrombus.

Indium-111 labeled platelet scintigraphy has been used successfully to identify intravascular thrombi in various locations[1–16] including the left ventricle in man.[7,8] This report defines the optimum time window after injection of the labeled platelet suspension for detection of cardiac thrombi, identifies the most useful imaging views, determines the reproducibility of the technique, and provides illustrations of representative positive and negative studies including those that may be misleading or difficult to interpret.

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Methods

The patient data base consists of 662 scintigraphic images obtained from 64 patients with left ventricular (LV) aneurysms (n = 38) or mitral valve disease (n = 23) and 3 patients with acute myocardial infarction who later died. Patients were imaged 7.5 ± 5.2 days (mean ± standard deviation [SD]) before aneurysmectomy, mitral valve replacement, or death. Of the 23 patients requiring mitral valve replacement, 3 had coronary artery bypass surgery and 8 had aortic valve replacement. Confirmation of the presence or absence of a thrombus was possible at surgery or autopsy in all studies. Injected platelets were labeled according to a method previously described.[7,17,18] Most patients were imaged in the left anterior oblique, right anterior oblique, anterior, and left lateral views on the day of injection of the platelet suspension and at least on alternate days thereafter for a maximum of 6

days. Patients were imaged on a large field-of-view gamma scintillation camera fitted with a medium energy collimator. The dual peak energy analyzers were centered on both photopeaks of indium-111 with 20% windows. In all patients, 200,000 counts over the field-of-view were obtained.

Analysis of data: Two retrospective analyses were performed. First, to determine optimum views and time windows for imaging, images were analyzed without knowledge of the surgical result, patient identity, view, and day from injection of the platelet suspension that the image was obtained. Three observers were used. They were instructed to make either a positive or a negative reading. A positive image was defined as an area of increased and abnormal activity in the region of the cardiac blood pool (Fig. 1). If the area of increased activity included the whole blood pool of the ventricle, images were read as negative (Fig. 2, panel 1). A series of representative negative images is shown in Figure 3. All images were read by the same observer on 2 different occasions. The 3 observers had varied academic backgrounds. Observer 1 was a computer person with extensive experience in nuclear cardiology. Observer 2 was a young faculty member with 6 months' experience in nuclear cardiology. Observer 3 was a cardiologist with an interest in nuclear medicine and the principal investigator. The data were decoded by a fourth investigator who was responsible for the analysis.

Image interpretation was categorized with respect to interpreted result (positive or negative), patient number (1 to 64), view (right anterior oblique, left anterior oblique, left lateral, and anterior), observer (1, 2, or 3), reading (1 and 2), and imaging window (days 0 to 2, 3 to 4, or 5 to 6 after injection of the platelet suspension). These categorized data along with the surgical results were entered into a file on a digital computer from which contingency tables were generated as desired. Sensitivity, specificity, and diagnostic accuracy were determined for each view and imaging time.

After analysis of these data, a second retrospective study was performed. Readers were blinded to patient identity and surgical or autopsy result and were unblinded for imaging time and views. Images from day 0 were compared with those from either day 3 or day 4. If the area of activity within the left ventricle increased from the day 0 image to the day 3 or 4 image, the study was considered positive. All doubtful images were read as negative. Sensitivity, specificity, and diagnostic accuracy were determined.

Surgical specimens were handled as follows: Findings at surgery were considered either thrombus positive or thrombus negative. In every case, this differentiation was unequivocal. Patients who had thrombi and who received injections within

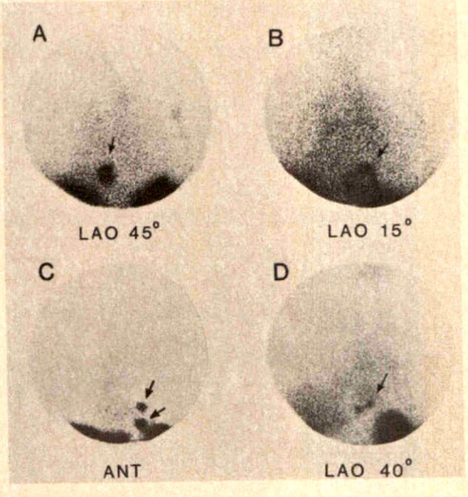

FIGURE 1. Scintiphotos obtained 72 hours after injection of the platelet suspension. Images are orientated with the top of the illustration cephalad. The increased activity in the right lower quadrant of each panel is from the spleen. The activity in the lower left quadrant in each panel is from the liver. The **arrows** point to areas of increased activity within the left ventricle and represent typical active thrombi within large anteroapical left ventricular aneurysms. These images were obtained from 4 different patients. ANT = anterior; LAO = left anterior oblique.

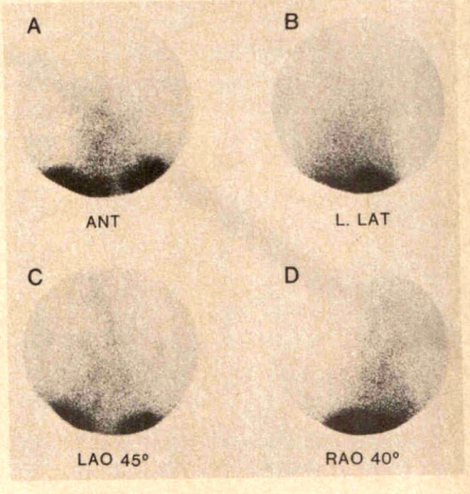

FIGURE 3. The orientation of this figure is the same as that in Figure 1. The area of increased activity in **panels A and C** in the right lower zone is due to the spleen and that in the left lower zone is due to the liver. In **panels B and D** there is superimposition of liver and splenic activity in the lower portions of both panels. This figure represents a typical series of negative images obtained 72 hours after injection of the platelet suspension. ANT = anterior; LAO = left anterior oblique; LLAT = left lateral; RAO = right anterior oblique.

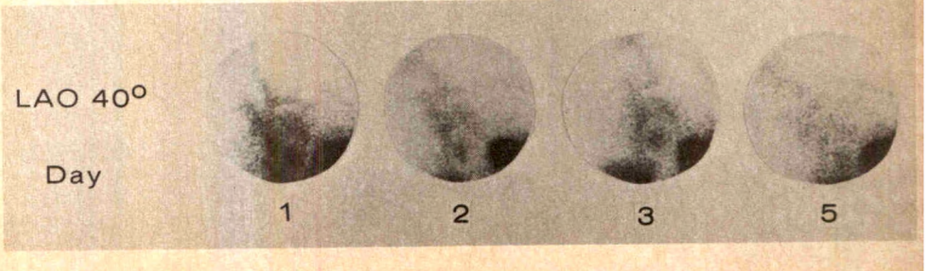

FIGURE 2. The orientation of these images is the same as in Figure 1. All images were obtained in the left anterior oblique (LAO) view on days 1, 2, 3, and 5 after injection of the platelet suspension. Note that the activity in the region of the left ventricle decreases with time.

8 days of surgery or autopsy had tissue levels of indium-111 measured. Thus, thrombus-positive patients were further subdivided, on the basis of surface thrombus indium-111 activity, into those with active and those with inactive disease. Inactive thrombi were arbitrarily categorized as those in which the surface activity was ≤6 times the adjacent blood activity normalized by mass. Three patients had inactive thrombi; in 3 others, tissue data could not be obtained. The data were analyzed by both including and excluding these 6 patients.

The reproducibility of the interpretations of the observers was assessed for each view and imaging window. The intraobserver agreement was calculated as the number of agreements between 2 different readings divided by the number of agreements plus the number of disagreements by the same observer.

The interobserver agreement was determined for each view and imaging window by dividing the number of agreements by the total number of images read.

Results

The sensitivity, specificity and diagnostic accuracy by view and imaging window for all observers and both readings are given in Figure 4. A total of 12 patients had LV thrombi at surgery or autopsy. The highest diagnostic accuracy was found in time period 3 to 4 days in the anterior (82 ± 1%, mean ± 1 SD, $p < 0.01$) and left anterior oblique views (85 ± 1.6%, $p < 0.01$). The specificity for all views in all time periods ranged from 97 ± 4% in the left anterior oblique view in the time period 0 to 2 days to over 98% in most of the other views in the various time windows. The sensitivity was highest in the left anterior oblique view in time period 3 to 4 days and was 54 ± 5% ($p < 0.01$). The significance values for the foregoing analysis was determined using the Duncan multiple range test.

By excluding patients with inactive thrombi from analysis, the following changes were seen (Fig. 5). The highest diagnostic accuracy was significantly ($p < 0.001$) enhanced to 88 ± 1.3% versus 82 ± 1% in the time period 3 to 4 days in the anterior view, and in the left anterior oblique (90 ± 2% versus 85 ± 2%), right anterior oblique (87 ± 4% versus 78 ± 3%, $p < 0.005$), and left lateral (87 ± 1% versus 78 ± 3%) views. The sensitivity was similarly enhanced in the 3 to 4 day time period in all views particularly the left anterior oblique view: anterior 57 ± 4% versus 44 ± 3%, $p < 0.001$; right anterior oblique 48 ± 5% versus 32 ± 3%, $p < 0.001$; left lateral 52 ± 5% versus 41 ± 4%, $p < 0.005$; and left anterior oblique view 67 ± 4% versus 54 ± 5%, $p < 0.001$. Specificity was unaltered at between 98 and 100%.

Because the foregoing indicates that the time period 3 to 4 days after injection of the platelet suspension was optimum for imaging, we combined the imaging views in that time period, considering a positive in any view as a positive. Sensitivity, specificity, and diagnostic accuracy were not altered. However, more reliable localization of increased activity to the left ventricle was possible using multiple views.

By comparing the 4 images on day 0 to those obtained on the third or fourth day of imaging, we could improve sensitivity and diagnostic accuracy to 65 ($p < 0.001$) and 90% (p not significant), respectively. Specificity was unaltered at 99%.

Overall intraobserver agreement was 91% with a range of 81% in the time period 0 to 2 days in the left anterior

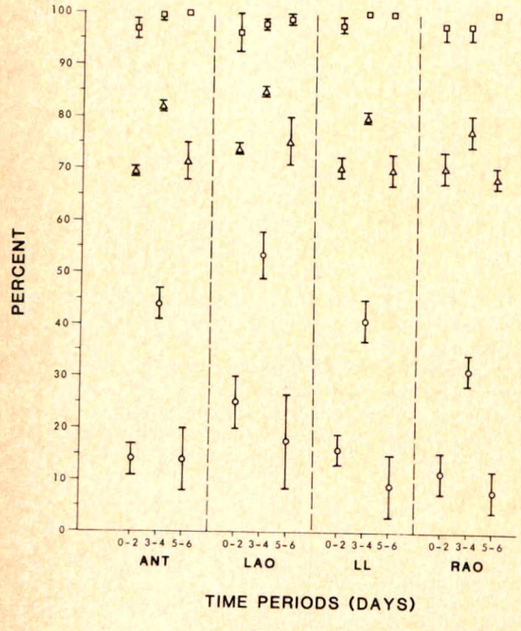

FIGURE 4. Percent sensitivity, specificity, and diagnostic accuracy in the anterior (ANT), left anterior oblique (LAO), left lateral (LL), and right anterior oblique (RAO) views for all images in time periods 0 to 2, 3 to 4, and 5 to 6 days. The data include patients with inactive thrombi. **Squares** = specificity, **triangles** = diagnostic accuracy, and **circles** = sensitivity. Mean ± standard deviation is for all observers and all readings (n = 6).

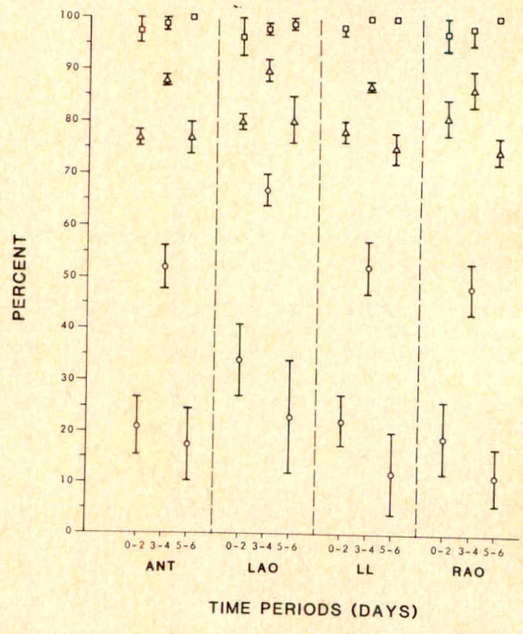

FIGURE 5. Analysis of these data is similar to that in Figure 4, except that inactive thrombi have been excluded. Inactive thrombi were defined as thrombi in which the surface indium-111 activity was ≤6 times the activity in the blood normalized by mass. Abbreviation as in Figure 4.

oblique view for observer 1, to 100% in the left lateral view in the time period 5 to 6 days for all observers. The interobserver agreement for reading 1 for all views and times ranged from 71 to 100%. For reading 2 the range was 77 to 100%. The mean interobserver agreement was 88%.

Discussion

In this retrospective analysis, we defined the diagnostic accuracy and reproducibility of indium-111 platelet scintigraphy in the diagnosis of LV thrombi. All 3 observers agreed that the left anterior oblique view in the time period 3 to 4 days after injection of the platelet suspension was the optimum time for imaging. By adding the right anterior oblique, left lateral, and anterior images to the left anterior oblique image, the parameters of accuracy were not significantly enhanced. However, imaging in multiple views allowed more reliable localization of thrombi to the left ventricle. There was significant enhancement of sensitivity and diagnostic accuracy when images from day 0 were compared with those obtained on the third and fourth day of imaging. Specificity remained high irrespective of the manner in which images were analyzed.

In a previous study in which multiple view images were acquired serially for 6 days and prospectively interpreted, the sensitivity was 71%.[19] In this retrospective analysis a comparison of day 0 with day 3 to 4 images resulted in a 65% sensitivity and a 67% decrease in imaging time with concomitant lowering of cost. Using day 0 with day 3 to 4 comparison, no reduction in specificity was noted.

There are 2 circumstances in which major difficulty occurs with the interpretation of images. Both are illustrated in Figures 2 and 6. In Figure 6, the patient had an elevated left hemidiaphragm with resultant elevation of the spleen, causing difficulty with interpretation of the anterior and right anterior oblique imaging views. The main point of differentiation is that activity due to the spleen characteristically accumulates early, that is, within minutes of injection of the platelet suspension, whereas increased activity due to a thrombus tends to be maximal 3 to 4 days after injection of the platelet suspension. To eliminate this difficulty, we advise interpretation of images only after a chest X-ray has excluded the presence of a raised left hemidiaphragm. Difficulty also might be encountered with the differentiation of increased blood pool activity due to a large LV volume or aneurysm, or both, from that due to a LV thrombus. Usually, increased activity from an enlarged blood volume is uniform in intensity, regular in shape, and much larger than the area normally occupied by a thrombus (Fig. 2). In addition, blood pool activity decreases with time, whereas activity due to a thrombus increases.

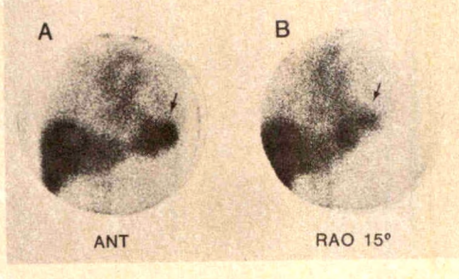

FIGURE 6. The orientation of this figure is the same as that of Figure 1. The activity in the left lower zone of both images is due to the liver. The **arrows** point to an area of increased activity that superficially resembles a thrombus but is due to the spleen which is raised as a result of an elevated left hemidiaphragm. ANT = anterior; RAO = right anterior oblique.

In most cases, the appearance of a thrombus is typical and little difficulty is experienced with its interpretation. Typical thrombi are illustrated in Figure 1. Most commonly, positive images are represented as a single hot spot (panel A, Fig. 1). Less commonly, multiple hot spots are seen (panel C, Fig. 1). The thrombus might be seen tangentially in which case a linear area of increased activity is seen (panel D, Fig. 1). In 2 patients, we have seen a circular increase in activity (panel B, Fig. 1), which is due to a laminated thrombus occupying most of the surface of the aneurysmal left ventricle. When scintiphotos (Fig. 1) are seen at any 1 time during the course of imaging, the interpretation is unequivocally positive. The strength of this technique is that it is highly specific.[7,8] Its limitation resides with its relatively low sensitivity. However, the series presented includes patients with chronic LV aneurysms and therefore old thrombi. We anticipate that studies designed to detect newly forming thrombi, as might occur during acute myocardial infarction, would be more sensitive than those in patients with chronic disease. This study also demonstrates that this technique is highly reproducible.

Apart from indium-111 platelet scintigraphy, several other noninvasive techniques have been used to identify LV thrombi. Two-dimensional echocardiography has the advantage of being suitable for repeated studies.[8,19–23] Its major limitation is image quality. Of the studies, 25% cannot be used for thrombus determination. With technically adequate studies, 2-D echocardiography carries a sensitivity and specificity of 77 and 93%.[19] Strict criteria should be used for clot detection. Either global or regional LV dysfunction must be present. The clot needs to be viewed in at least 2 transducer positions. The clot blood interface is usually echogenic, with the interior of the thrombus demonstrating a variable degree of echogenicity. Computerized tomography has recently been proposed as a means of identifying clot.[24,25] Image quality has improved with newer generation equipment. Motion artifact has been reduced. Preliminary studies are promising, but studies defining its diagnostic accuracy have not yet been reported. It is possible that platelet scintigraphy, a highly specific test that reflects thrombus activity, might be used to complement either 2-dimensional echocardiography or computerized tomography. Both of these later techniques reflect thrombus mass. Radionuclide angiography may also be used to detect intraventricular thrombi. It is widely available and like 2-dimensional echocardiography may be used in the simultaneous evaluation of global and regional LV function.[26]

In summary, the following are recommended concerning the imaging of LV thrombi using indium-111 labeled platelets. Imaging should only be performed on the day of injection and 3 or 4 days thereafter. On both imaging days, the left anterior oblique, right anterior oblique, left lateral, and anterior views should be used to facilitate the localization of LV thrombi, which is particularly important when studying patients during acute myocardial infarction when the possible sites of thrombi are multiple. All images should be interpreted only after chest X-ray has excluded the coexistence of a raised left hemidiaphragm.

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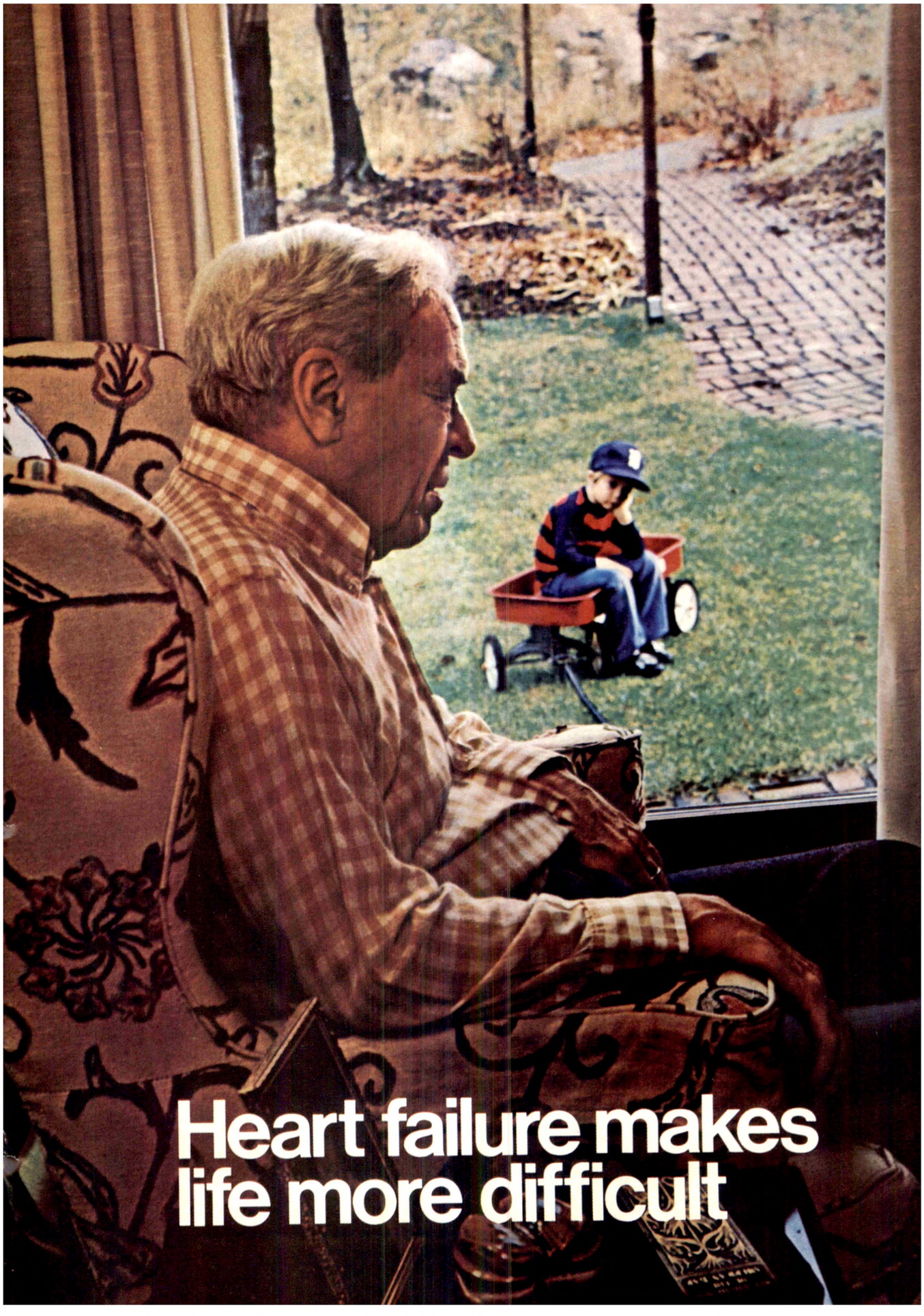
Heart failure makes
life more difficult

CAPOTEN®
(captopril tablets)
makes living
easier

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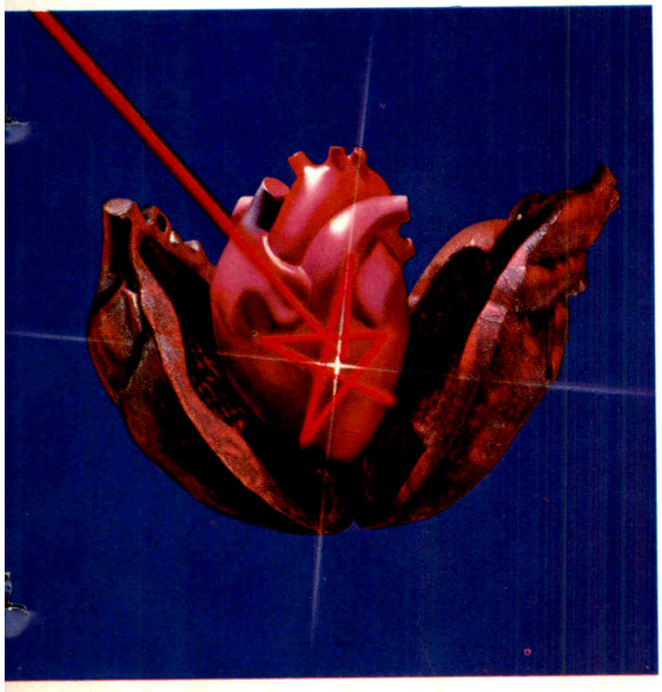
With the availability of CAPOTEN, heart failure† patients can enjoy an enhanced quality of life. Because, in patients who require more than digitalis and diuretics, CAPOTEN can improve their hemodynamic profile[1] and provide an opportunity to feel better.

- Eases principal heart failure symptoms[1]
- Restores patients' sense of well-being[1]
- Increases patients' capacity for exercise,[1] allowing them to participate more fully in the physical activities of everyday life



ACE* INHIBITOR

CAPOTEN®
(captopril tablets)

Can make the difference between merely existing and actively living

†CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

*Angiotensin Converting Enzyme

Please see brief summary of prescribing information on last pages of this advertisement.

ACE*INHIBITOR

CAPOTEN®
(captopril tablets)

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

*Angiotensin Converting Enzyme

†Please see brief summary of prescribing information on last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Data on file, Squibb Institute for Medical Research.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by

 (Continued on next page.)

(continued from preceding page)

antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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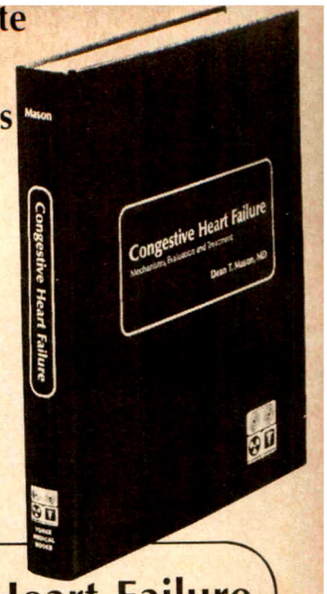

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Dean T. Mason, M.D.

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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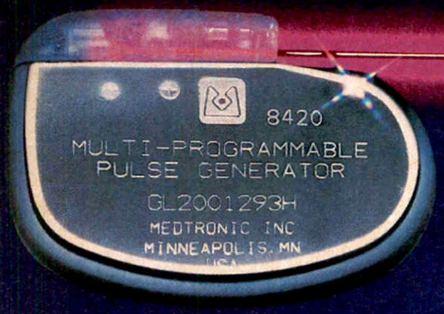

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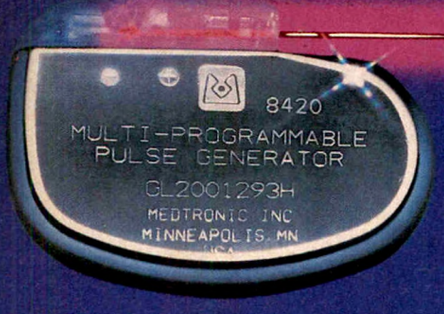

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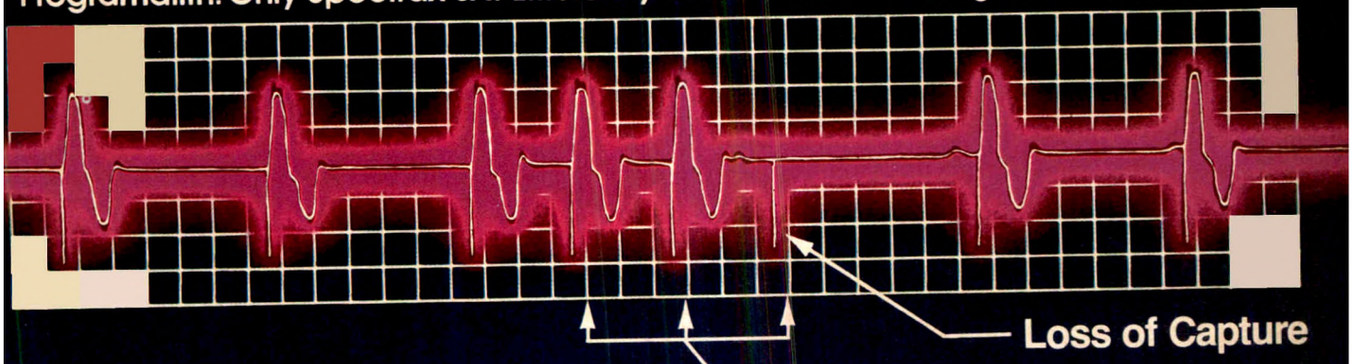

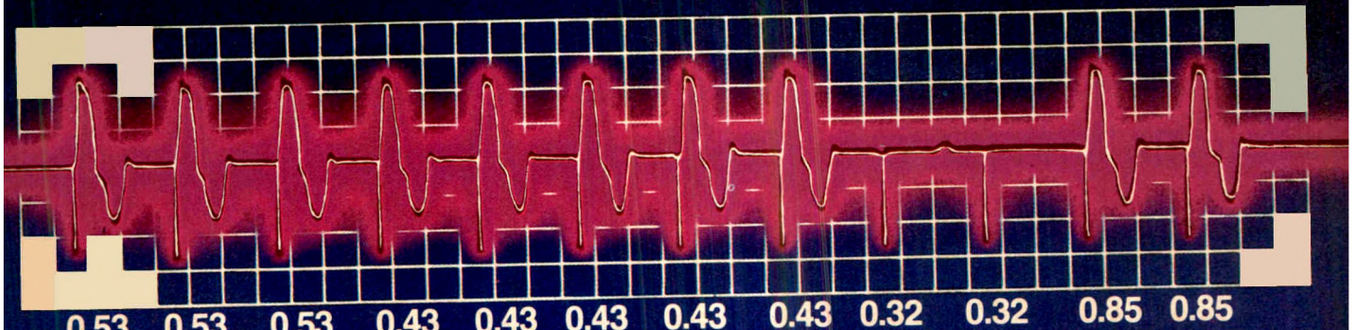


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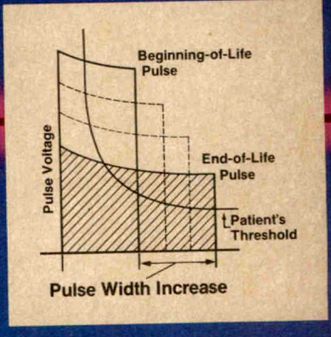

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Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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is now

Once-a-day

New dosage schedule: To start, 100 mg once-a-day, or in divided doses
Dosage range: 100 mg – 450 mg daily

Lower doses (especially 100 mg) may not maintain full effect at end of 24-hour period. Measure BP near end of dosing interval, adjust to larger or more frequent dosage if needed.

*exerts a relative preference for beta-one receptors; this preference is not absolute

100-mg tablets

Please turn page for brief Prescribing Information.

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536-5763-A

A127

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings *Cardiac Failure:* Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions *Impaired Hepatic or Renal Function:* The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

C83-16 (Rev. 5/83)

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Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

536-5763-A

Tissue Digoxin Concentrations During the Quinidine-Digoxin Interaction

NATALIE J. WARNER, MD, EDWARD B. LEAHEY Jr., MD, THOMAS J. HOUGEN, MD, J. THOMAS BIGGER Jr., MD, and THOMAS W. SMITH, MD

Digoxin concentrations in serum, myocardium, 3 separate skeletal muscles, kidney, liver, and 5 sites in the brain were measured in 26 dogs given 12-alpha ^{3}H-digoxin. Ten of the dogs also received 200 mg of quinidine sulfate orally 3 times daily for 3 days, and 6 others received 240 mg of quinidine gluconate intravenously every 3 hours for 24 hours. Mean serum quinidine concentration was 6.7 ± 1.5 μg/ml in the dogs treated with quinidine for 24 hours and 3.6 ± 2.3 in the dogs treated with quinidine for 3 days ($p < 0.01$). Mean serum digoxin concentrations were 2.72 ± 0.88 ng/ml in dogs treated with digoxin only, 2.61 ± 0.45 in dogs treated with quinidine for 24 hours (difference not significant [NS]), and 3.20 ± 0.92 in dogs that received quinidine for 3 days (NS). In dogs treated with quinidine for 3 days, serum digoxin concentration correlated significantly with serum quinidine concentration ($r = 0.76$), indicating that quinidine did affect the serum digoxin concentration. No differences in tissue digoxin concentrations were found between either of the groups of dogs that received quinidine and the group that received digoxin alone. Tissue-to-serum digoxin concentration ratios were significantly different in 4 of the tissues studied in the group of dogs that received quinidine for 24 hours. In this group, the ratio of myocardial-to-serum digoxin concentration was higher ($p < 0.01$) and ratios of renal ($p < 0.05$), occipital muscle ($p < 0.01$), and medullary brainstem ($p < 0.01$) digoxin concentrations were lower. The ratio of renal-to-serum digoxin concentration decreased as serum quinidine concentration increased ($r = -0.63$). No correlation was found between serum quinidine concentration and tissue-to-serum digoxin concentration ratio for other tissues.

Thus, in contrast to the findings in a previous study, there is no evidence of increased concentration of digoxin in the brain or of decreased digoxin concentration in the myocardium when quinidine is given to dogs receiving digoxin. The relationship of serum-to-tissue digoxin concentration changes in some tissues after 24 hours of quinidine administration. The decrease in the ratio of renal-to-serum digoxin concentration suggests that the decrease in renal digoxin clearance with quinidine is due to failure of digoxin to enter the kidney rather than to a block in the excretion of digoxin present in the kidney.

The serum digoxin concentration is used to infer cardiac concentrations of digoxin[1] and probable effects of digoxin on cardiac rhythm and contractility.[2,3] When quinidine is given with digoxin, the serum digoxin concentration increases as a result of decreases in digoxin clearance and volume of distribution.[4–8] Displacement of digoxin from binding sites in tissue, including myocardium, has been suggested as the mechanism of the quinidine-induced decrease in digoxin volume of distribution.[4–6,9] In order to manage patients receiving both digoxin and quinidine, it is important to know whether the relationship between serum digoxin concentration and myocardial digoxin concentration and effect is changed by quinidine.

Previous studies of the effects of quinidine on tissue concentrations of digoxin include a study of skeletal muscle digoxin concentration in patients and 2 studies done in animals. Schenck-Gustafsson et al[10] reported that the ratio of skeletal muscle-to-serum concentration of digoxin decreased in 8 of 10 patients after 4 days of

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quinidine treatment. The decrease in skeletal muscle digoxin concentration completely accounted for the observed decrease in digoxin volume of distribution. Kim et al[11,12] gave intravenous tritiated digoxin to guinea pigs with and without simultaneous quinidine infusion. The serum digoxin concentration in animals given quinidine was higher than that of animals infused with digoxin alone, indicating that quinidine decreased the tissue uptake of digoxin. Doherty et al[13] gave tritiated digoxin to 11 dogs, 6 of which also received quinidine. The concentration of digoxin in the myocardium was lower in the quinidine-digoxin group than in the digoxin group. The mean serum digoxin concentration of the quinidine-digoxin group was also lower and there was no difference in the myocardial-to-serum digoxin concentration ratio.

The present study determines the effect of quinidine on tissue digoxin concentrations and on the ratio of tissue digoxin concentration-to-serum digoxin concentration in dogs.

Methods

Experimental preparation: Digoxin specifically labelled at the 12-alpha position with 0.2 μCi of tritium per microgram of digoxin was given to 26 mongrel dogs of either sex (14 to 27 kg) in doses of 40 μg/kg intravenously on day 1 and 20 μg/kg intravenously on days 2 and 3. Ten of the dogs received only digoxin. Ten received digoxin plus quinidine sulfate, 200 mg orally 3 times per day for the 3 days of the study. We used these regimens because preliminary studies in our laboratory showed that they produced steady-state serum drug concentrations. In an attempt to achieve higher and more predictable serum quinidine concentrations and to investigate the tissue digoxin concentration in the early phase of the quinidine-digoxin interaction, we gave 6 additional dogs 240 mg of quinidine gluconate intravenously every 3 hours for 24 hours after the third and final dose of digoxin. Tissue samples were obtained on day 4, 18 to 24 hours after the final dose of digoxin.

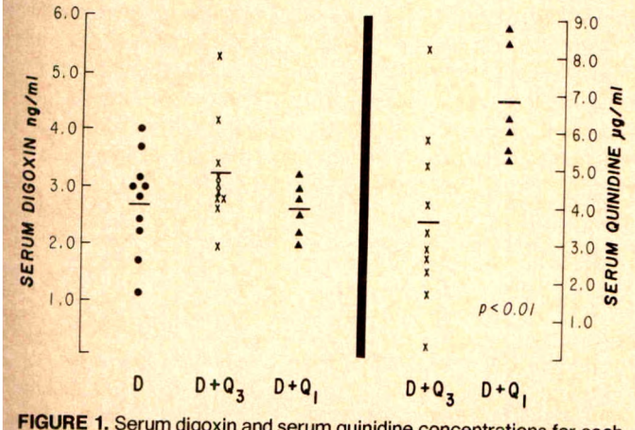

FIGURE 1. Serum digoxin and serum quinidine concentrations for each group of experimental animals. Dogs that received digoxin only are represented by **circles** and labelled D. Dogs that received digoxin and quinidine for 3 days are represented by **crosses** and labelled D + Q3, and dogs that received digoxin for 3 days and quinidine for 24 hours are represented by **triangles** and labelled D + Q1. Dogs that received intravenous quinidine for 24 hours had a mean serum quinidine concentration of 6.7 ± 1.5 μg/ml, which was significantly higher ($p < 0.01$) than the mean serum quinidine concentration of 3.6 ± 2.3 μg/ml of the dogs that received 3 days of oral quinidine. There were no statistically significant differences in mean serum digoxin concentration between any of the groups of dogs. Dogs that received digoxin alone had a mean serum digoxin concentration of 2.72 ± 0.88 ng/ml (standard deviation), dogs that received 24 hours of quinidine had a mean serum digoxin concentration of 2.61 ± 0.45 ng/ml, and dogs that received 3 days of quinidine had a mean serum digoxin concentration of 3.20 ± 0.92 ng/ml.

Tissue analysis: Serum samples were obtained from each dog immediately before it was killed. Three samples of approximately 50 mg each were obtained from the myocardium, 3 separate skeletal muscles (occipital, intercostal, and quadriceps femoris), kidney, liver, cerebral cortex, cerebellum, hypothalamus, pons, and medulla. Tissue samples were blotted dry, weighed, and dissolved by overnight incubation at 45°C in 0.5 ml of Protosol™ (New England Nuclear). Glacial acetic acid (0.02 ml) was added to each sample to make it less alkaline. After addition of scintillation medium (TT21, Yorktown Research), the samples were stored in the dark at 4°C for 1 week to reduce chemiluminescence. Duplicate samples of 500 μl of serum were added to scintillation medium and also stored in the dark for 1 week. Samples were counted in a liquid scintillation counter until there was no difference between 1 set of counts and the next, indicating that there was no remaining chemiluminescence. To permit correction for quenching, an internal standard containing approximately 5,000 cpm of tritiated digoxin was added to each sample and samples were again counted until there was no difference in counts per minute on successive determinations. By comparison with the counts per minute obtained from a known concentration of tritiated digoxin, the tissue or serum digoxin concentration was calculated in nanograms per gram of wet tissue weight or nanograms per milliliter of serum. The average digoxin concentration of the 3 samples from each tissue was calculated for each dog and used in the statistical analysis.

Serum quinidine concentration was measured by high pressure liquid chromatography after extraction by the method of Cramer and Isaksson.[14]

Statistical analysis: The ratio of tissue-to-serum digoxin concentration was calculated by dividing tissue digoxin concentration by the dog's serum digoxin concentration. Means and standard deviations of serum and tissue digoxin concentrations and of the tissue-to-serum digoxin concentration ratios were calculated for each tissue in all 3 groups of dogs. Student's t test was used to compare the mean serum quinidine concentrations of the 2 groups of dogs that received quinidine and to compare the mean serum digoxin concentration of each of the quinidine-treated groups to the mean serum digoxin concentration of the group that received digoxin alone. Hotelling's t test, a multivariate t test designed to avoid the possibility of making type I statistical errors by performing repeat t tests,[15] was used to compare tissue concentrations of digoxin between each of the groups of dogs that received quinidine and the group that received digoxin alone. Regression analysis was used to correlate serum digoxin concentration and tissue-to-serum digoxin concentration ratios with serum quinidine concentrations.

Results

Serum digoxin and quinidine concentrations: Serum quinidine and digoxin concentrations for the experimental animals are shown in Figure 1. The mean serum quinidine concentration was 3.6 ± 2.3 μg/ml (mean ± standard deviation) in the group that received 3 days of oral quinidine and 6.7 ± 1.5 μg/ml in the dogs that received intravenous quinidine for 24 hours. Despite the wide between-animal variability in the group

that received oral quinidine, these values are significantly different at the $p < 0.01$ level. Unexpectedly, no difference was found in the mean serum digoxin concentration between either group of dogs that received quinidine and the group that received only digoxin. The 10 dogs that received digoxin alone had a mean serum digoxin concentration of 2.72 ± 0.88 ng/ml. The average serum digoxin concentration in the 6 dogs that received digoxin and quinidine for 24 hours was 2.61 ± 0.45 ng/ml. The dogs that received quinidine sulfate for 3 days had an average serum digoxin concentration of 3.20 ± 0.92 ng/ml. Despite the fact that the mean is higher in this group than in either of the other 2 groups, there was wide between-animal variability in serum digoxin concentration in this group and there was no statistically significant difference between the mean serum digoxin concentration of this group and the mean serum digoxin concentration of the group that received digoxin only.

Figure 2 shows the relationship of serum digoxin concentration to serum quinidine concentration for the 10 dogs that received digoxin and 3 days of quinidine. There is a positive linear regression of serum digoxin concentration on serum quinidine concentration, indicating that a drug interaction between quinidine and digoxin occurred. No such relationship was seen between serum quinidine concentrations and serum digoxin concentrations in the dogs that received 24 hours of quinidine.

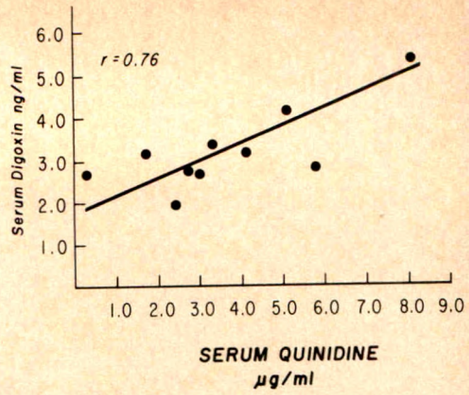

FIGURE 2. Serum digoxin concentration plotted against serum quinidine concentration as the independent variable for the 10 dogs that received 3 days of quinidine. The correlation coefficient for these 2 variables is 0.76 ($p < 0.01$).

Tissue digoxin concentrations: Table I shows the mean tissue digoxin concentration for each tissue type in the 3 groups of dogs. The tissue digoxin concentration varied widely from tissue to tissue. Kidney tissue samples had the highest digoxin concentration, followed by the heart, liver, skeletal muscle, and brain samples. We found no statistically significant differences in mean tissue digoxin concentrations between either of the 2 groups of dogs treated with quinidine and the group treated with digoxin alone.

Table I also shows the ratios of tissue-to-serum digoxin concentration for each tissue in the 3 experimental groups. Similar ratios of tissue-to-serum digoxin concentration have been reported in animals and patients treated with digoxin.[16–19] We found no significant differences in these ratios between dogs that received digoxin alone and those that received digoxin and quinidine for 3 days. However, there were differences in the ratio of tissue-to-serum digoxin concentration between the dogs that received digoxin alone and dogs that received digoxin and 1 day of intravenous quinidine. Using Hotelling's t test, which simultaneously tests the equality of the means of several variables, the chance that the tissue-to-serum ratios for the digoxin only and the digoxin and 24-hour quinidine group were equal was $p < 0.01$. (We used a critical value of $p < 0.05/2 = p < 0.025$ because we did 2 separate Hotelling's t tests.) Further analysis showed that there were differences between the 2 groups in 4 of the tissue-to-serum digoxin concentration ratios. Myocardial-to-serum digoxin concentration ratio was higher in dogs that received quinidine for 24 hours than in dogs that received digoxin only ($p < 0.01$). In contrast, the ratio of tissue-to-serum digoxin concentration was significantly lower in the kidney ($p < 0.05$), occipital muscle ($p < 0.01$), and the medullary portion of the brainstem ($p < 0.01$).

TABLE I Tissue Digoxin Concentrations and Tissue-Serum Concentration Ratios

	Tissue Digoxin (ng/g Wet Weight)			Tissue-Serum Digoxin		
	Digoxin	Digoxin + Quinidine, 3 Days	Digoxin + Quinidine, 1 Day	Digoxin	Digoxin + Quinidine, 3 Days	Digoxin + Quinidine, 1 Day
Heart	86 ± 27	114 ± 58	111 ± 26	33 ± 8*	35 ± 9	42 ± 5*
Kidney	1,090 ± 710	1,080 ± 346	627 ± 220	436 ± 277†	349 ± 113	236 ± 53†
Skeletal muscle						
Quadriceps	17 ± 5	21 ± 6	16 ± 7	6.4 ± 1.4	6.7 ± 1.5	6.3 ± 1.9
Occipital	22 ± 6	24 ± 7	16 ± 2	8.3 ± 1.6*	7.8 ± 1.5	6.4 ± 1.0*
Intercostal	16 ± 5	22 ± 6	16 ± 6	6.1 ± 1.3	7.0 ± 1.8	6.1 ± 2.6
Brain						
Cortex	5 ± 2	7 ± 4	8 ± 5	1.9 ± 0.8	2.1 ± 1.1	3.2 ± 0.7
Cerebellum	10 ± 3	12 ± 5	9 ± 3	4.0 ± 2.4	3.9 ± 1.7	3.4 + 0.9
Pons	9 ± 2	14 ± 7	9 ± 5	3.9 ± 1.8	4.7 ± 2.1	3.4 ± 1.7
Hypothalamus	9 ± 5	8 ± 5	5 ± 2	3.6 ± 2.5	2.6 ± 1.5	2.0 ± 1.0
Medulla	11 ± 4	20 ± 11	5 ± 2	4.4 ± 2.1*	6.4 ± 3.7	2.1 ± 1.0*
Liver	62 ± 34	74 ± 52	72 ± 22	24 ± 11	22 ± 11	27 ± 4

* $p < 0.01$.
† $p < 0.05$.

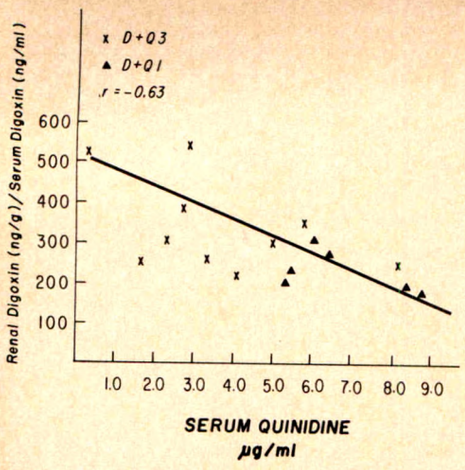

FIGURE 3. The ratio of renal-to-serum digoxin concentration plotted on the ordinate as the dependent variable against the serum quinidine concentration as the independent variable on the abscissa for all of the dogs that received quinidine. Dogs that received quinidine for 3 days are represented by **crosses.** Dogs that received quinidine for 24 hours are represented by **triangles.** The correlation coefficient between these 2 variables is -0.63 ($p < 0.05$). D + Q1 = digoxin for 3 days and quinidine for 24 hours; D + Q3 = digoxin and quinidine for 3 days.

We performed regression analysis on concentration ratio for these 4 tissues using serum quinidine concentration as the independent variable. There was no correlation between serum quinidine concentration and the ratio of tissue-to-serum concentration of digoxin for myocardial, skeletal muscle, or medullary brainstem. Figure 3 shows the relationship between renal-to-serum digoxin ratio and serum quinidine concentration. As the serum quinidine concentration increased, the ratio of renal to serum digoxin concentration decreased ($r = -0.63$, $p < 0.05$).

Discussion

Despite the fact that we could not demonstrate a statistically significant difference in mean serum digoxin concentration between either of the groups of dogs that received quinidine and the group that received digoxin only, we have evidence for the existence of a quinidine-digoxin interaction in both of these groups. Previous studies have shown a relationship between serum quinidine concentration and the magnitude of the effect of quinidine on serum digoxin concentration.[17] In the group of dogs that received quinidine for 3 days, regression analysis with serum quinidine concentration as the independent variable and serum digoxin concentration as the dependent variable (Fig. 2) showed a regression (serum digoxin concentration = 2.1 + 0.31 × serum quinidine concentration). Differences in tissue digoxin concentrations between the group of dogs that was treated with quinidine for 24 hours and the group treated with digoxin only was evidence that the quinidine-digoxin interaction was occurring after 24 hours of quinidine administration.

We did not confirm the findings of Doherty et al,[13] who reported that the concentration of digoxin in the myocardium was lower and the concentration of digoxin in the brain was higher in dogs that received digoxin and quinidine than in dogs that received digoxin only. Interpretation of both our study and that of Doherty et al is limited by the lack of a statistically significant difference in serum digoxin concentration between dogs treated with digoxin and quinidine and dogs treated with digoxin alone. We did find that the dogs that received 24 hours of high-dose intravenous quinidine (but not those that received 3 days of quinidine) had a statistically significantly higher ratio of myocardial-to-serum digoxin concentration than did the dogs that received digoxin only. Further work is necessary to determine the explanation for this finding.

Skeletal muscle accounts for 40 to 50% of the body digoxin stores in both dogs and humans.[10,17] A small change in the concentration of digoxin in the skeletal muscle would decrease the volume of distribution of digoxin sufficiently to explain the change in serum digoxin concentration seen with quinidine.[10] Neither of our quinidine regimens produced an increase in serum digoxin concentration (we did not directly measure volume of distribution) and we are unable to support the hypothesis that quinidine decreases digoxin volume of distribution and thereby increases serum digoxin concentration by displacing digoxin from skeletal muscle.

Quinidine causes a decrease in the renal clearance of digoxin, which occurs within hours of quinidine administration.[5–8,18–20] We measured the concentration of digoxin in the kidney after 24 hours of quinidine administration and found that it is less than expected based on the serum digoxin concentration. This finding suggests that decreased binding or uptake of digoxin by renal tubular cells, rather than a block in excretion of digoxin present in the kidney, accounts for the quinidine-induced decrease in renal clearance of digoxin. Previous studies have shown that the quinidine-induced decrease in the renal clearance of digoxin is quinidine dose-dependent.[7] When all 16 dogs that received quinidine in this study are considered together, there is a significant negative correlation between serum quinidine concentration and the ratio of renal-to-serum digoxin concentration.

In summary, this study reports the tissue concentrations and tissue-to-serum concentration ratios of digoxin during the quinidine-digoxin interaction in dogs. After drug doses calculated to produce steady-state serum drug concentrations, there were no differences in tissue digoxin concentrations or tissue-to-serum digoxin concentration ratios between dogs treated with quinidine and dogs treated with digoxin alone. Specifically, in contrast to a previous study,[13] we found no evidence that myocardial digoxin concentration was lower or brain digoxin concentration was higher with quinidine. In dogs that received 24 hours of intravenous quinidine, the ratio of myocardial digoxin concentration-to-serum digoxin concentration was higher and the ratios of renal, medullary brainstem, and occipital muscle-to-serum digoxin concentration were lower than in dogs that received digoxin only. The mechanism of the quinidine-digoxin interaction remains to be delineated further in studies in which the serum digoxin concentration increases substantially during quinidine treatment.

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Effect of Atrial Fibrillation on Atrial Blood Flow In Conscious Dogs

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This study was undertaken to examine the independent effects of atrial tachycardia, ventricular tachycardia, and atrial fibrillation (AF) on atrial and ventricular blood flow in conscious, heart-blocked dogs using radioactive microspheres. Atrial blood flow averaged 0.54 ± 0.08 ml/min/g during the control period at an atrial rate of 124 beats/min and a ventricular rate of 90 beats/min. Atrial flow increased to 0.72 ± 0.12 ml/min/g during atrial pacing at 236 beats/min, but was not significantly altered by ventricular pacing at 200 beats/min. AF at a ventricular rate of 90 beats/min resulted in atrial flow values of 0.91 ± 0.08 ml/min/g. The ratio of atrial flow to left ventricular flow during AF averaged 1.18 ± 0.08. Administration of a maximal vasodilating dose of adenosine during AF further increased atrial flow to 2.18 ± 0.16 ml/min/g. Atrial tachycardia or AF did not significantly affect ventricular blood flow. These data indicate (1) that atrial blood flow increases significantly during AF, reaching flow values per gram of tissue comparable to those of the left ventricle, and (2) that this flow is regulated by the metabolic needs of the atrial tissue and does not represent maximal vasodilation.

The observation that coronary blood flow is regulated in direct response to metabolic need has been well established for the ventricular[1,2] as well as the atrial[3,4] myocardium. In conscious, heart-blocked dogs Neill et al[3] found that a change in atrial contraction rate from 92 to 201 beats/min increased atrial blood flow from 0.38 to 0.75 ml/min/g of tissue, thus establishing that atrial blood flow increases with increasing contraction rate, and is presumably the result of increased metabolic activity. White et al[4] observed in anesthetized dogs that atrial fibrillation (AF), with its more rapid and asynchronous pattern of contraction, increased atrial blood flow 2- to 3-fold above control values. These investigators also observed that rapid atrial pacing was a less potent stimulus for increasing atrial blood flow than was AF.[4]

The present study was designed to assess the independent effects of atrial and ventricular tachycardia and of acute AF on atrial and ventricular blood flow in a conscious dog model with complete heart block. This animal model eliminated the hemodynamic changes observed in open-chest preparations, and allowed the changes which normally occur in systemic hemodynamics due to the various interventions to be minimized. To test whether this blood flow increase represented maximal atrial vasodilation, adenosine was administered during AF. From these data, the relative maximal vasodilating capacity of atrial and ventricular vascular beds was determined.

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Methods

Surgical preparation: Eleven adult mongrel dogs, weighing 20 to 28 kg, were anesthetized with sodium thiamylal (25 to 30 mg/kg, intravenously). After endotracheal intubation, respiration was maintained with an Emerson model 3-PV respirator. A left thoracotomy was performed through the fifth intercostal space. A heparin-filled polyvinyl chloride catheter (3.0 mm, outside diameter) was introduced into the arch of the aorta by way of the left internal mammary artery. The pericardium was opened and the heart was suspended in a pericardial cradle. A Medtronics model 6917A sutureless unipolar pacing lead and a bipolar pacing lead constructed in our laboratory were implanted on the free wall of the right ventricle. Complete heart block was produced by injection of <1 ml of 40% formaldehyde into the His bundle, using a modification of the method of Steiner and Kovalik.[5] The unipolar pacing electrode was tunnelled through the sixth intercostal space and the ventricular rate was maintained subsequently at 80 beats/min using a Medtronics model 5995

rate-adjustable ventricular inhibited pulse generator implanted in a subcutaneous pouch. A second bipolar pacing lead was implanted on the right atrial appendage. Additional heparin-filled polyvinyl chloride catheters were inserted into the left ventricle through the apex and into the left atrium by way of the left atrial appendage. The catheters and bipolar pacing electrodes were tunnelled dorsally into a second subcutaneous pouch but were not exteriorized until the day of the study to protect them from damage. The chest was closed, the pneumothorax evacuated, and the animal extubated. The implanted pacemaker was used to maintain heart rate throughout the postoperative period.

Experimental procedure: Studies were carried out 7 to 10 days after the initial surgery. All dogs were active and appeared to be in good health, were afebrile, and had hematocrits ranging from 38 to 46%. The dogs were placed on the study table on their right sides, and the laboratory was kept dimly illuminated. The subcutaneous pouch containing the catheters and pacing electrodes was anesthetized with 2% lidocaine infiltration. The catheters and wires were exteriorized through a 1 cm skin incision. The incision was closed in 2 layers around the catheters and wires, then sealed with Aeroplast spray dressing to prevent development of an acute pneumothorax. The ventricular rate was set at 90 beats/min using a Medtronics model 9600A rate controller and was left at that rate for the remainder of the study. The right ventricular bipolar electrode was connected to a Grass model S44 stimulator. The atrial pacing electrode was connected to a Digitimer model 3290 stimulator. The aortic, left ventricular, and left atrial catheters were cleared and connected to Statham model P23Db pressure transducers. All pressure measurements were referenced to zero at the mid-chest level. Data were recorded with a Hewlett-Packard model 3955-D magnetic tape recorder and model 7700 eight-channel direct-writing thermal recorder.

Microsphere technique: Regional myocardial blood flow and cardiac output were estimated by injecting 8 to 10 μm carbonized microspheres labelled with the gamma-emitting radionuclides cerium-141, chromium-51, scandium-46, strontium-85, and niobium-95 into the left atrium. Microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran solution. This stock solution was diluted in 10% dextran solution so that 1.0 ml contained approximately 3,000,000 microspheres. The microspheres were mixed before injection by alternate agitation for at least 15 minutes in an ultrasonic bath and a Vortex agitator. Approximately 1.1 ml of microsphere suspension was drawn up into a preweighed 3 ml syringe, several drops of this suspension were placed into each of 5 preweighed plastic counting vials, and the syringe containing the microsphere suspension was reweighed. Blood flow measurements were made with approximately 1.0 ml of microsphere suspension injected over a 5 second interval into the left atrial catheter and the catheter was flushed with 10 ml of normal saline solution. A reference sample of arterial blood was collected into 6 plastic counting vials from the aortic catheter at a constant rate of approximately 20 ml/min by a withdrawal pump, beginning simultaneously with the microsphere injection and continuing for 90 seconds.

Experimental protocol: The atrial pacing rate was adjusted to obtain the slowest rate at which the atria could be paced without evidence of any escape beats; the ventricular rate was 90 beats/min. A microsphere injection was performed under these conditions to provide the control data. The atrial pacing rate then was increased at least 100 beats/min over the rate used during control conditions and another microsphere injection was performed. The atrial pacing rate was returned to its control value and the ventricular rate was increased to 200 beats/min by pacing the bipolar right ventricular electrode and thus inhibiting the implanted pacemaker. A microsphere injection was performed under these conditions. Bipolar pacing of the right ventricle was terminated and the ventricular rate returned to 90 beats/min and remained at that rate for the rest of the study. AF was induced by rapid (20 Hz) bipolar stimulation of the right atrial pacing electrode. In 8 dogs, AF was maintained spontaneously after a 5-min period of rapid atrial pacing; 3 dogs required continuous pacing at 20 Hz to maintain AF. A microsphere injection was made when AF or rapid atrial pacing had been present for at least 15 minutes. In 6 of the 11 dogs included in this report, an intravenous infusion of adenosine (1 mg/kg/min) was instituted while AF was present. A microsphere injection was performed under these conditions when all hemodynamic variables had been stable for at least 5 minutes.

Tissue preparation: The animals were killed at the end of data collection by intravenous administration of 30 mg/kg sodium thiamylal followed by 40 mEq of potassium chloride. The heart was removed and the atria were carefully dissected from the ventricular and venous tissues. The atria were separated into 3 pieces representing the right atrial free wall, the left atrial free wall, and the interatrial septum. Each atrial piece was weighed to the nearest 0.1 g. The left and right ventricles were separated and weighed to the nearest gram. All tissue was fixed in 10% buffered formalin for at least 24 hours. The 3 atrial pieces were cut into multiple small sections each weighing approximately 0.5 g. Care was taken to identify any samples that exhibited tissue damage due to formaldehyde injection and these samples were excluded from the blood flow determinations. Ten transmural samples weighing approximately 1 g were obtained from the free wall of the right ventricle midway between the apex and the pulmonary outflow tract. Each of these transmural samples was divided into an epicardial and an endocardial portion. The left ventricle, including the ventricular septum, was sectioned into 4 transverse rings of approximately equal thickness. The 2 middle rings were divided radially into 7 anatomic sections. Each radial section was further subdivided into 4 transmural layers of approximately equal weight from the epicardium (layer 1) to the endocardium (layer 4). Each tissue sample was weighed to the nearest milligram and was placed in a separate plastic vial for subsequent gamma counting.

Calculation of myocardial blood flow and cardiac output: Each tissue sample and the reference blood samples were counted for 10 minutes in a Packard model A5912 gamma spectrophotometer. Counts were accumulated in predetermined energy range windows selected to maximize activity from a given isotope while minimizing spillover from the other isotopes used in the study. Spillover ratios for each isotope into the lower energy windows were determined from locally prepared standards and used to correct the raw tissue counts obtained in each window by the standard stripping technique described by Rudolph and Heyman.[6] Total blood flow to each myocardial tissue sample (Q_m) in milliliters/minute was calculated using the formula: $Q_m = Q_r \cdot C_m/C_r$, where Q_r is the reference blood sample flow rate (milliliters/minute), C_m is the corrected count activity in the myocardial tissue sample, and C_r is the total count activity in the reference blood sample. Total myocardial tissue sample blood flow was divided by the corresponding tissue sample weight and expressed as milliliters/minute/gram of tissue.

Cardiac output (Q_{co}, milliliters/minute) was determined from the relation: $Q_{co} = Q_r \cdot C_i/C_r$, where Q_r and C_r are as defined previously and C_i is the total amount of activity injected into the left atrium. C_i was determined in the following manner: the 5 plastic counting vials containing several drops of microsphere suspension were reweighed and the weight of microsphere suspension in them was determined by subtraction. The empty syringe from the microsphere injection and the 5 vials were counted in the gamma spectrophotometer

TABLE I Anatomic Data

Body weight (kg)	24 ± 1 (11)
Right ventricular weight (g)	45 ± 2 (11)
Left ventricular weight (g)	111 ± 5 (11)
Right atrial free wall weight (g)	7.1 ± 0.5 (8)
Interatrial septum weight (g)	2.7 ± 0.1 (8)
Left atrial free wall weight (g)	6.2 ± 0.5 (8)
Total atrial weight (g)	16.0 ± 0.7 (8)
Left ventricular/body weight ratio (g/kg)	4.6 ± 0.2 (11)
Left atrial/body weight ratio (g/kg)	0.27 ± 0.02 (8)
Right atrial/right ventricular weight ratio	0.28 ± 0.02 (8)
Left atrial/left ventricular weight ratio	0.06 ± 0.01 (8)

Values are means ± standard error. Numbers in parentheses indicate the number of dogs in which these values were measured. Atrial free wall weights were used in ratio computations. Left ventricular weight includes the interventricular septum.

for 10 minutes each. An estimate of the counts/milligram of microsphere suspension was obtained by dividing the total number of counts in each vial by the weight of the microsphere suspension in that vial. The average counts/milligram for the 5 vials was determined and then multiplied by the difference between the full and empty syringe weights to obtain an estimate of the total number of counts contained in the syringe before injection. The total number of counts remaining in the empty syringe was subtracted from this value to determine C_i, the total number of counts injected into the left atrium. The coefficient of variation of the average counts/milligram of microsphere suspension was <5% for each injection. The percentage of the total number of counts contained in the full syringe that was injected into the left atrium ranged from 85 to 94%.

Data analysis: Right atrial free wall flow values were computed by averaging the data obtained from the individual right atrial samples. A similar procedure was used to obtain flow values for the left atrial free wall and the interatrial septum. In addition, a combined atrial flow value was obtained by computing the average flow for all atrial samples, including the interatrial septum. The endocardial/epicardial blood flow ratio for each left ventricular radial section was computed by dividing the blood flow value obtained for layer 1 into the value for layer 4. Data for all right ventricular samples were averaged to provide the right ventricular blood flow values; similarly, all left ventricular data values were averaged to obtain the left ventricular blood flow values. Thus, each dog contributed to the final analysis a single data value for each anatomic region for each intervention, irrespective of the actual number of atrial or ventricular tissue samples that were obtained.

Atrial rate, ventricular rate, aortic pressure, and left atrial pressure were measured from the graphic output obtained at the time of microsphere injection. These data were averages over several respiratory cycles before administration of microspheres and again after completion of reference blood sample collection. Atrial and ventricular vascular resistance indexes were computed by dividing the mean arterial pressure by the myocardial blood flow values determined by the microsphere technique.

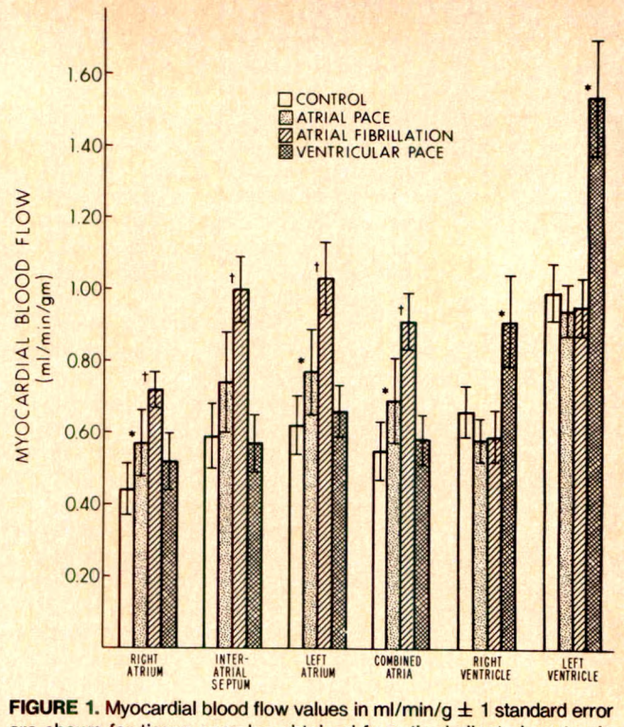

FIGURE 1. Myocardial blood flow values in ml/min/g ± 1 standard error are shown for tissue samples obtained from the indicated anatomic regions during the control period and during the interventions of atrial pacing, AF, and ventricular pacing. **Asterisks** denote a mean value that was significantly different ($p < 0.05$) from the control value; **daggers** denote a mean value during AF that was significantly different from the value obtained during atrial pacing.

Statistical analyses were carried out using multiple paired t tests. When appropriate, the Bonferroni method of adjusting the critical value of t for multiple comparisons was employed.[7] Throughout this report, a p value <0.05 was considered to represent a significant difference between 2 mean values.

Results

Specific anatomic weights and computed weight ratios for the atria and ventricles of the dogs included in this report are shown in Table I.

Hemodynamic data obtained in 11 dogs during control conditions and during the interventions of atrial

TABLE II Hemodynamic Data

	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	Mean Aortic Pressure (mm Hg)	Left Ventricular End-Diastolic Pressure (mm Hg)	Cardiac Output (liters/min)
Control	124 ± 5	90 ± 1	95 ± 4	5 ± 1	3.0 ± 0.2
Atrial pace	236 ± 4*	90 ± 1	92 ± 4	4 ± 1	2.7 ± 0.2
AF	. . .	89 ± 1	94 ± 4	3 ± 1*	2.2 ± 0.2*
Ventricular pace	124 ± 5	199 ± 1*	98 ± 3†	. . .	3.2 ± 0.3

Values are means ± standard error of 11 dogs.
* Significantly different ($p < 0.05$) from control values.
† Significantly different ($p < 0.05$) from atrial pace and AF values.

pacing, AF, and ventricular pacing are summarized in Table II. Mean aortic pressure was 95 ± 4 mm Hg during the control period, and did not change significantly from the control value as a result of the interventions. Cardiac output was not changed from its control value by either atrial or ventricular pacing; however, a significant 26% decrease in cardiac output was observed during AF. Mean left atrial pressure was 4 ± 1 mm Hg during the control period and during the pacing interventions; a slight but significant decrease in mean left atrial pressure to 3 ± 1 mm Hg was observed during AF.

Atrial and ventricular blood flow data obtained in 11 dogs during control, atrial pacing, AF, and ventricular pacing are shown in Figure 1. Transmural distribution of flow in both the right and left ventricle was not affected by the atrial pacing interventions; thus, only combined values for ventricular flow are given. During the control period, right atrial flow averaged 0.44 ± 0.07 ml/min/g and was significantly lower than the average left atrial flow value of 0.62 ± 0.08 ml/min/g. Thus, right atrial flow per gram of tissue was approximately 71% of the corresponding flow in the left atrial tissue. In the combined atrial samples, atrial pacing significantly increased atrial blood flow by 28%, from 0.54 ± 0.08 to 0.72 ± 0.12 ml/min/g. AF further increased atrial blood flow to 0.91 ± 0.08 ml/min/g which represents a significant 26% increase over the blood flow observed during atrial pacing at 236 beats/min. This pattern of an increase in atrial flow with atrial pacing and a further increase with the onset of AF was observed in the individual samples obtained from the right atrium, left atrium, and interatrial septum. Further analysis of these data revealed that with AF the dogs fell into 2 distinct groups. In 1 group (6 dogs) there were no discrete atrial contractions that resulted in any change in atrial pressure; in the second group (5 dogs) discrete atrial pressure changes ranging from 1 to 3 mm Hg were generated at a rate of 500 to 800/min. In those dogs in which no discrete pressure changes were observed, the atrial flow increased an average of 0.47 ± 0.06 ml/min/g from the control value. In those dogs in which discrete pressure variations were observed, the atrial flow increased 0.25 ± 0.10 ml/min/g from the control value. While the difference in these 2 mean values failed to reach statistical significance ($p = 0.08$) it strongly suggests that AF without a definite organized atrial contraction induces a greater increase in atrial flow than occurs when a synchronized rapid atrial pressure wave is produced. Neither atrial pacing nor AF significantly changed the blood flow to the right or left ventricular tissue samples from that observed during the control period. A 39% increase in right ventricular and a 55% increase in left ventricular blood flow was observed with ventricular pacing at 200 beats/min compared with the control value. The left ventricular endocardial/epicardial blood flow ratio was 1.32 ± 0.03 during the control period and increased slightly but significantly to 1.47 ± 0.06 during ventricular pacing. However, ventricular pacing did not significantly alter blood flow to the atrial tissue samples in any of the regions examined.

These changes in atrial blood flow relative to ventricular blood flow can be examined further by computing several blood flow ratios. Figure 2 shows the right atrial/right ventricular, left atrial/left ventricular, and right atrial/left atrial blood flow ratios during the control period and during the interventions of atrial pacing, AF, and ventricular pacing. The left atrial/left ventricular blood flow ratio was 0.61 ± 0.05 at control, increased to 0.77 ± 0.06 with atrial pacing, and increased further to 1.18 ± 0.08 with AF. With ventricular pacing the ratio decreased to 0.43 ± 0.02. The right atrial/left atrial flow ratio was 0.69 ± 0.04 in the control period and did not change significantly with any of the interventions.

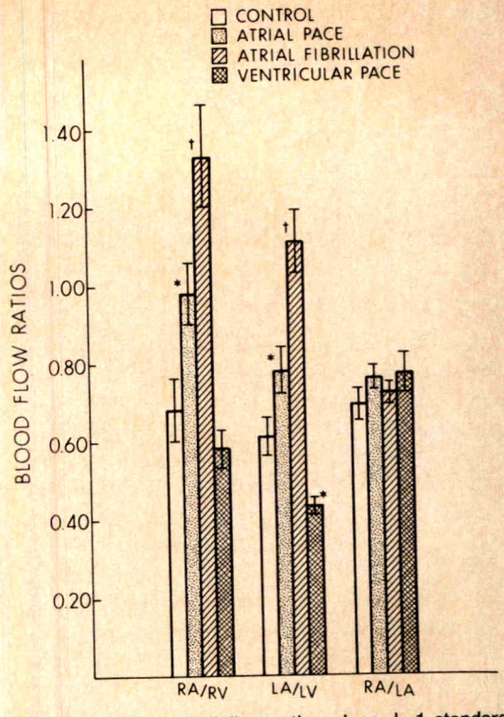

FIGURE 2. Myocardial blood flow ratio values ± 1 standard error computed between the indicated anatomic regions during the control period and during the interventions of atrial pacing, AF, and ventricular pacing. **Asterisks** denote a mean value that was significantly different ($p < 0.05$) from the control value; **daggers** denote a mean value during AF that was significantly different ($p < 0.05$) from the value obtained during atrial pacing. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

The hemodynamic effects of a maximal vasodilating dose of adenosine in 6 dogs are shown in Table III. In the presence of AF, adenosine administration decreased

TABLE III Hemodynamic Effects of Adenosine Administration During Atrial Fibrillation

	Control	AF Only	AF With Adenosine
Mean aortic pressure (mm Hg)	96 ± 2	96 ± 4	70 ± 3*
Left ventricular end-diastolic pressure (mm Hg)	3 ± 1	2 ± 1	4 ± 1
Cardiac output (liters/min)	3.0 ± 0.3	2.1 ± 0.3	3.0 ± 0.2*

Values are means ± standard error of 6 dogs.
* Significantly different ($p < 0.05$) from AF by paired *t* test.

TABLE IV Vascular Resistance Indexes (mm Hg/ml/min)

	Control	AF	AF With Adenosine
Combined atria	208 ± 27	125 ± 11*	38 ± 5†
Right ventricle	156 ± 21	198 ± 36	31 ± 21†
Left ventricle	103 ± 10‡	121 ± 17	25 ± 8†‡

Values are means ± standard error of 6 dogs.
* Significantly different from control value.
† Significantly different from control and AF values.
‡ Significantly different from corresponding combined atria value.

mean aortic pressure from 96 ± 4 to 70 ± 3 mm Hg. Cardiac output increased 45% from its value during AF alone and reached a value (3.0 ± 0.2 liters/min) that was not significantly different from the cardiac output observed during the control period. Left atrial pressure was not altered by adenosine administration. Atrial and ventricular blood flows during the control period and during AF with and without adenosine are shown in Figure 3. With adenosine administration, atrial blood flow increased 146% from the value observed during AF alone. This atrial blood flow value of 2.18 ± 0.16 ml/min/g represents a 303% increase over the corresponding control value. For comparison, left ventricular blood flow increased from a control value of 1.02 ± 0.11 to 4.09 ± 0.27 ml/min/g with adenosine administration during AF. Thus, adenosine administration resulted in a 300% increase in ventricular blood flow.

Vascular resistance indexes computed for the control period and during AF with and without adenosine are shown in Table IV. Administration of adenosine during AF resulted in a 69 ± 4% decrease in the atrial resistance index while the right and left ventricular resistance indexes decreased 85 ± 4% and 80 ± 3%, respectively. This 69% atrial resistance index decrease is significantly lower than the 85% and 80% decrease in the ventricular vascular resistance indexes. Note that the vascular resistance index for the left ventricle is significantly less than for the combined atria during both the control period and during vasodilation secondary to AF and adenosine administration.

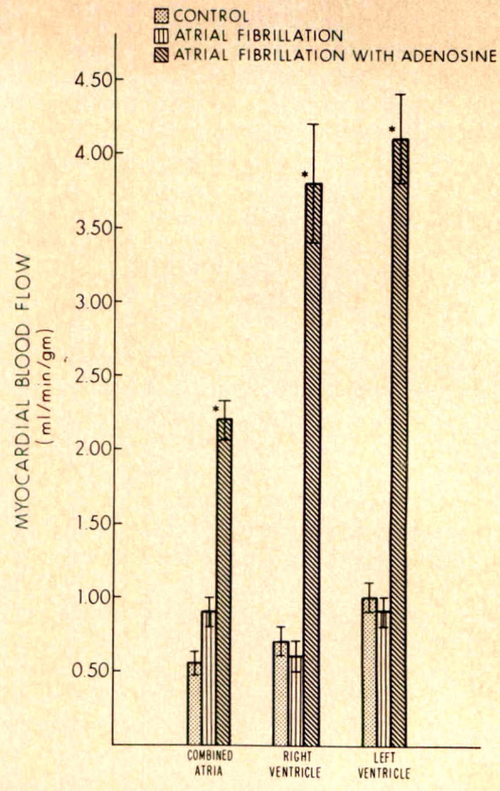

FIGURE 3. Myocardial blood flow values in ml/min/g ± 1 standard error are shown for tissue samples obtained from the indicated anatomic regions during the control period and during AF with and without adenosine. **Asterisks** denote a mean value obtained during AF with adenosine administration that was significantly different ($p < 0.05$) from the corresponding value obtained during AF alone. Note the change in scale from Figure 1.

Discussion

This study was carried out in conscious dogs to avoid the effects of acute surgical trauma and thus obtain the data in as physiologic a preparation as possible. Complete heart block was created so that a constant ventricular rate of 90 beats/min could be maintained during atrial pacing and AF, keeping the perfusion pressure of the atrial and ventricular vascular beds constant. As shown in Tables II and III, mean aortic pressure remained within a range of 6 mm Hg, except when adenosine was administered.

During the control period, atrial pacing at 124 beats/min resulted in atrial contractions that generated atrial pressure increases ranging from 2 to 12 mm Hg in all dogs. Atrial pacing at 236 beats/min also resulted in discrete atrial contractions that generated comparable pressure increases. During AF, the group of 5 dogs which exhibited discrete atrial pressure changes did not increase their atrial blood flow as much as the group of 6 dogs which exhibited no discrete atrial pressure changes. Thus, it seems fair to conclude that atrial blood flow is determined, at least in part, by the frequency of atrial contraction. In addition, Neill et al[3] observed in heart-blocked dogs that atrial vasomotion is independent of ventricular vasomotion, as demonstrated by the fact that atrial blood flow did not increase in response to ventricular pacing. This observation was confirmed in the present study.

The increased flow observed during AF could have resulted from an acute increase in atrial size, resulting in an increase in atrial wall stress. Atrial geometry was not measured in the studies included in this report. However, mean left atrial pressure was slightly decreased during AF and, unless there is a marked decrease in atrial compliance, it is unlikely that the atrium was larger. Henry et al,[8] using echocardiographic determinations of left atrial size in human subjects, observed no change in atrial size before and after an episode of paroxysmal AF.

In the present experiment it was not possible to obtain samples of atrial venous blood; therefore, we cannot directly address the question of whether the increased flow observed during AF represents a true increase in metabolic demand. However, White et al,[4] using a microspectrophotometric method in anesthetized dogs,

observed that the atrial O_2 extraction averaged 61% in their experiment when sinus rhythm was present and was not altered by AF. Thus, it is reasonable to assume in our dogs that the metabolic demands of the atrial muscle are significantly increased during AF and that these demands are met primarily in increasing blood flow. In a study which compared ventricular blood flow in the empty beating heart to the empty fibrillating heart, Kleinman and Wechsler[9] observed that an 82% increase in flow occurred when ventricular fibrillation was induced. This change is comparable to the 69% increase in atrial blood flow observed during AF.

It is important to know if the elevated blood flow observed during AF represents maximal atrial vascular vasodilation or if this vascular bed is simply regulating its blood flow at a level consistent with its metabolic demand. In the present study, administration of a maximal vasodilating dose of adenosine during AF resulted in a 146% increase in atrial blood flow from that observed during AF alone. This observation would indicate that atrial blood flow during AF is not maximal and thus appears to be under active vasomotor control.

The data obtained in our studies and in the study of White et al[4] clearly demonstrate that the acute onset of AF induced by electrical stimulation is associated with a significant increase in atrial flow. This does not answer the question of whether chronic AF is associated with a similar increase in atrial blood flow and, hence, it is somewhat premature to speculate on the clinical importance of these measurements. On the other hand, if the chronically fibrillating atria can be shown to maintain a high metabolic need per gram of tissue, especially in the hypertrophied atrium, then the presence of a flow-limiting stenosis proximal to the branching of the atrial arteries may create a hemodynamic impairment that has not been appreciated previously. That is, the increase demand for flow in the atria may act to further reduce the already compromised amount of flow available for ventricular perfusion, and hence accelerate symptomatic coronary artery disease.

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Relation of Left Ventricular Mass to Geometry of the Proximal Coronary Arteries in the Dog

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Proximal epicardial coronary artery luminal diameters were measured from silicone casts formed in situ in freshly excised hearts under a constant pressure of 100 mm Hg. Twenty-five coronary arteries from 15 normal dogs and 22 coronary arteries in 13 dogs with either chronic pressure or volume overload hypertrophy were studied. Mean left ventricular (LV) body weight ratios were 4.75 ± 1.01 g/kg in the normal dogs, 8.4 ± 1.7 g/kg in the pressure-overload dogs, and 6.2 ± 0.6 g/kg in the volume-overload dogs. The cross-sectional area of the left circumflex (LC) coronary artery was determined at 11 branch sites. The ratio of the area of the branches to the area of the parent vessel was 1.095 ± 0.105, indicating that the cross-sectional area after a branch point increased.

A poor correlation existed between LV mass and coronary artery diameter in both normal and hypertrophy groups for the LC ($r = 0.44$), the left anterior descending (LAD) ($r = 0.63$), and the combined LC and LAD ($r = 0.52$). The mean cross-sectional area of the combined LC and LAD was 0.12 cm^2 in the normal group and 0.15 cm^2 in the hypertrophy group; this increase was not statistically significant ($p = 0.13$). When the mean cross-sectional area of the combined vessels was adjusted for heart weight, there was a decrease in the cross-sectional area/100 g of myocardium in the hypertrophy group compared with the control group. These data demonstrate that coronary artery luminal diameter in the dog does not increase commensurately with the increase in mass associated with myocardial hypertrophy.

The luminal diameter of the proximal coronary arteries is a major determinant of blood flow velocity. Shear stress at the blood-endothelial interface is directly proportional to blood flow velocity and is inversely proportional to the radius of the lumen.[1] Since myocardial blood flow increases proportionately with increasing ventricular mass,[2] the relation between coronary luminal diameters and left ventricular (LV) mass is of interest. In order for proximal blood flow velocity and hence the shear stress to remain unchanged in the presence of LV hypertrophy, the coronary arteries would have to increase in size commensurately with the increase in LV mass. If the coronary artery luminal diameters did not increase proportionately, the proximal blood flow velocity and shear stress would increase in the arteries supplying hypertrophied ventricles.

The dimensions of the epicardial coronary arteries at branch points also significantly influence coronary blood flow. The relation between the cross-sectional area of a vessel proximal to its branches and the total cross-sectional area of the branches determines the resistance to flow encountered at the branch site. The relation between the cross-sectional area of coronary arteries before and after major branching points has not been determined previously.

The purposes of the present study were (1) to examine the relation between proximal coronary artery luminal diameters and LV mass in chronic LV hypertrophy, and (2) to compare the dimensions of coronary arteries relative to the size of their major branches.

Methods

Thirteen dogs with chronic LV hypertrophy were studied. Ten had a modified coarctation-banding procedure[3] performed midway between the aortic valve and innominate artery at 7 weeks of age. The puppies recovered and were allowed to mature for 17 ± 8 months (mean ± standard deviation

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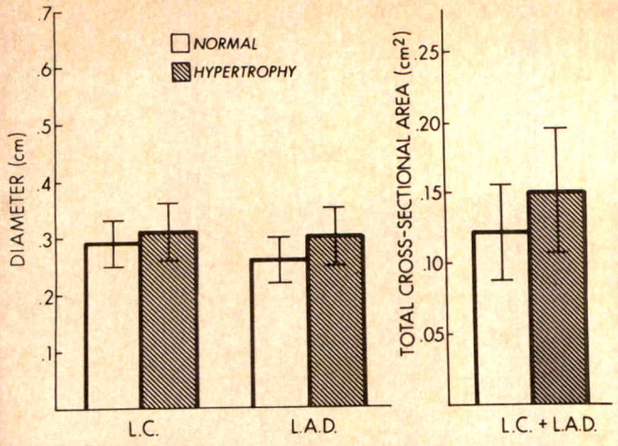

FIGURE 1. Comparison of left circumflex (LC) coronary artery diameter ($p = 0.64$), left anterior descending coronary artery diameter (LAD) ($p = 0.05$), and total cross-sectional area (LC + LAD) ($p = 0.13$) in normal and hypertrophied ventricles.

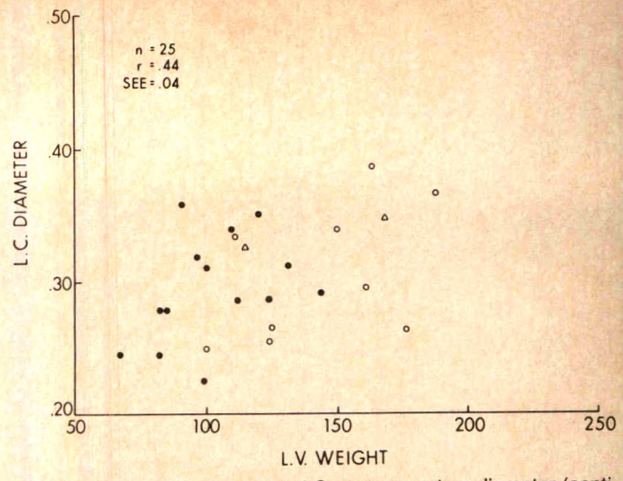

FIGURE 2. Correlation between LC coronary artery diameter (centimeters) and LV weight (grams). **Closed circles,** normal; **open circles,** modified coarctation-banding hypertrophy dogs; **triangles,** other hypertrophy dogs. SEE = standard error of the estimate.

[SD]) before being studied. The average arterial pressure measured proximal to the coarctation at the time of study was 182/88 mm Hg and the LV to body weight ratio (R) at the time of the study was 8.4 ± 1.7 g/kg.

The remaining 3 dogs in the hypertrophy group were adult mongrel dogs who underwent surgical procedures resulting in chronic volume overload hypertrophy ($r = 6.2 \pm 0.6$). In 2 of these dogs, a single chorda tendineae was surgically excised. The third adult dog had an aorto-caval fistula created between the abdominal aorta and the inferior vena cava. The average time interval from the surgery to the study in these 3 dogs was 15 ± 10 months.

Fifteen healthy adult mongrel dogs with a wide range of body weights ($r = 4.7 \pm 1.01$) served as controls.

After each dog was killed under barbiturate anesthesia by a lethal dose of potassium chloride, the heart and great vessels were removed and submerged in a bath of 0.9% normal saline solution. The left main coronary artery was cannulated from the ostium with an 8 cm section of high-pressure tubing connected by a 3-way stopcock to a Statham P23Db pressure transducer. Care was taken not to disturb the normal tethering of the vessel and there was no dissection around it. After the coronary arteries were flushed with saline solution, they were infused immediately with RTV-41 liquid silicone (General Electric) combined with adequate diluent and catalyst to ensure even flow and rapid solidification. The liquid silicone was infused until a continuous distending pressure of 100 mm Hg was achieved to approximate the mean diastolic pressure. The pressure was held constant until the silicone solidified. The coronary arteries then were removed from the heart and the vascular tissue was stripped from the silicone casts. The right ventricle, atria, and valvular tissues were excised and the stripped LV weights were recorded.

The diameters of the coronary artery casts were measured with a vernier caliper at a point just proximal to the first marginal branch of the left circumflex (LC) artery and at a point just proximal to the first diagonal branch of the left anterior descending (LAD) coronary artery. The diameter was measured 3 times at 2 perpendicular points around the circumference of each vessel and averaged to obtain the mean diameter.

The mean diameters (d) of 2 major proximal branches of the LC coronary artery casts from 4 normal dogs and 3 dogs with hypertrophy also were measured with a vernier caliper. Measurements were made within 1 mm of the branching point from the parent vessel. The diameter of the parent vessel just proximal and distal to the origin of the branch also was obtained. The cross-sectional areas (CSA) of the vessels at these points then were determined using the following relation: $CSA = \pi(d/2)^2$. The branching ratio of each branch site was computed as the combined cross-sectional areas of the 2 branches divided by the cross-sectional area of the parent vessel proximal to the branch.

To test for possible volume changes after solidification, liquid silicone was allowed to solidify in a volumetric container and was shown to maintain a constant volume after hardening. Standard parametric statistical techniques were employed to evaluate the data.

Results

The mean diameters of the proximal LAD and LC coronary arteries in the normal and hypertrophied hearts are shown in Figure 1. Although the hypertrophied hearts had increased coronary artery diameters, only the LAD coronary artery was significantly different ($p = 0.05$) from the coronary artery diameter of the normal dogs. When the LAD and the LC coronary arteries were combined to obtain the total cross-sectional area of the main vessels that supply the left ventricle in dogs, there was no significant difference between the normal and hypertrophy groups ($p = 0.13$).

The correlation between proximal coronary luminal diameter and LV weight in the normal and hypertrophied hearts is shown for the LC artery in Figure 2 and for the LAD artery in Figure 3. The total cross-sectional area of the combined vessels is plotted against the LV weight in Figure 4. Although there is a weak positive correlation in each of the comparisons, indicating a trend for a greater coronary diameter in the bigger hearts, a high degree of scatter among the data was found. This trend is apparent both for the normal dogs in whom a wide range of heart weights was obtained and the dogs with LV hypertrophy. When the total cross-sectional area of both vessels (Fig. 4) is adjusted per 100

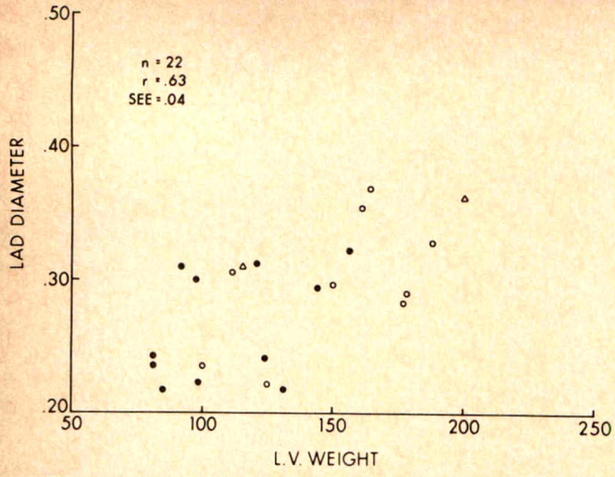

FIGURE 3. Correlation between LAD coronary artery diameter (centimeters) and LV weight (grams). **Closed circles,** normal; **open circles,** modified coarctation-banding hypertrophy dogs; **triangles,** other hypertrophy dogs. SEE = standard error of the estimate.

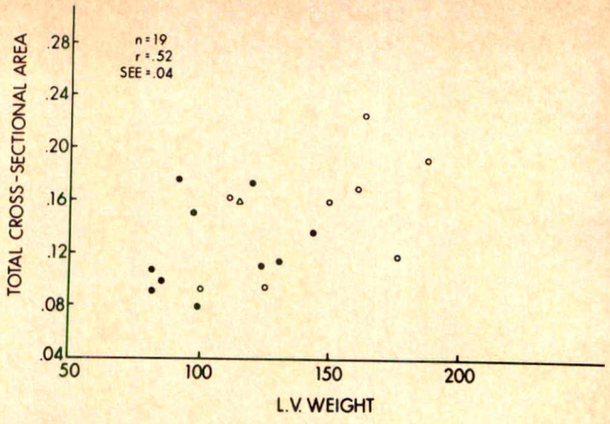

FIGURE 4. Correlation between total cross-sectional area (centimeters squared) and LV weight (grams). **Closed circles,** normal; **open circles,** modified coarctation-banding hypertrophy dogs; **triangles,** other hypertrophy dogs. SEE = standard error of the estimate.

g of LV myocardial weight, there is a decrease in the relative size of the vessels from hypertrophied hearts (9.91 mm^2/100 g) compared with those from the normal hearts (11.4 mm^2/100 g).

Eleven branching ratios were calculated from the first or second (or both) major branches in 7 typical circumflex casts. Four were from the normal group and 3 were from the hypertrophy group. The mean branching ratio was 1.095 ± 0.105 (mean ± SD). This ratio was significantly greater than unity, $p = 0.014$, indicating that the total cross-sectional area of the vessel increased after a branching point. This result was found in all 7 dogs, whether they were in the normal or the hypertrophy group.

Histologic evaluation of the proximal coronary arteries fixed under physiologic pressure was carried out in 8 additional dogs with either pressure or volume overload hypertrophy and compared with those from 2 normal dogs. There was no evidence of abnormal thickening or fibrosis of either the intimal or medial layers.

TABLE I Coronary Size Corrected for Heart Weight in Normal and Hypertrophied Ventricles

Study	Normal Group	Hypertrophy Group
Roberts and Roberts[4]	1.61*	1.31
Paulsen et al[5]	4.69†	3.19
Wilens et al[6]	7.0‡	5.1
Current study	11.4§	9.91

Comparison of the result of 3 previous studies and the current study. Note that there is a decrease in cross-sectional area of the vessels per 100 g of myocardium in the hypertrophy group in each study when the results are adjusted for heart weight.

* Mean cross-sectional area of LC, LAD, and right coronary arteries (mm^2/100 g [heart weight]).

† Sum of left and right coronary ostia (mm^2/100 g [heart weight]).

‡ External coronary surface area (cm^2/100 g [heart weight]).

§ Total cross-sectional area LC and LAD coronary arteries (mm^2/100 g [stripped left ventricular weight]).

Discussion

Proximal coronary blood flow velocity is determined by the coronary blood flow and the cross-sectional area of the proximal coronary arteries. The present study shows that while there is a trend toward an increase in coronary artery luminal diameter with LV hypertrophy, it is not proportional to the increase in LV mass. Since the blood flow per gram of myocardium during resting conditions either remains the same or is slightly increased in enlarged ventricles,[2] the proximal coronary blood flow, blood flow velocity, and intimal shear stress all must be increased in LV hypertrophy.

Previous studies comparing the size of the major coronary arteries with myocardial mass using various techniques generally have reported a trend toward an increase in luminal cross-sectional area with increased heart size. Whether or not the coronary arteries increase in size parallel to the increase in myocardial muscle mass has remained controversial.[4–6] One way to examine this question is to compare the coronary diameter in normal and hypertrophied hearts per 100 g of myocardium supplied by the vessels. A comparison of the results of 3 previous studies, when adjusted for the reported heart weights, and the results of the current study are shown in Table I. When the mean cross-sectional area of the vessels is corrected for the heart weight in normal and hypertrophied hearts, there is a decrease in the cross-sectional area of the vessels per 100 g of myocardium with increased myocardial mass. This indicates that the small increase in coronary size that occurs with increased heart size is not proportional to the increase in myocardial mass.

To test whether this decrease in relative coronary size is physiologically significant, the intimal shear stress in the proximal circumflex coronary artery of a small (75 g) and a hypertrophied (150 g) ventricle was calculated using blood flow data previously reported from our laboratory.[2] The cross-sectional area of the LC artery of a 75 g and 150 g heart was determined from the data in Figure 2. The predicted shear stress at the blood intimal interface in the individual vessels may be obtained

from the following equation[1]: $\tau = 4\zeta\bar{V}/r_i$, where τ is the shear stress, ζ is the blood viscosity in poises, $\bar{V}$ is the mean blood velocity, and r_i is the internal radius of the vessel. Increases in shear stress are directly proportional to increases in mean blood flow velocity and inversely related to the internal radius of the vessel. Estimations of the intimal shear stress in the representative 75 g and 150 g hearts for the LC coronary artery are 9.6 and 16.1 dynes/cm^2 respectively. This shear stress would be expected to increase still further under conditions of increased blood flow, such as with exercise or other physiologic stress. For example, the average peak blood flow recorded during reactive hyperemia in similar hypertrophy dogs in our laboratory is 302 ± 72 cm^3/min.[2] This degree of flow results in a markedly elevated shear stress of 62.9 dynes/cm^2 when calculated for a 150 g heart.

The relation of the cross-sectional area of a coronary artery to that of its major branches has not been determined previously. The average ratio of the change in total cross-sectional area due to branching (branching ratio) found in the present study was 1.095. By applying a similar analysis to the data of Patel et al,[7] who studied the relation between the aorta and its major divisions, an average branching ratio of 1.11 is obtained. Blum,[8] who studied the mesenteric arterial system, compared the mass of parent and branching vessels. He calculated an average branching ratio of 1.26 in the excised postmortem state and a ratio of 1.38 when the vessel segments were stretched to the in situ length.

The change in resistance to blood flow after branching into vessels of equal size is given by the relation[9]: $P_1/P_2 = d^2/n$, where P_1 represents the pressure gradient (proportional to the vascular resistance) before a bifurcation, P_2 is the pressure gradient distal to the bifurcation, d is the branching ratio, and n is the number of branches. Therefore, for any bifurcation (n = 2), the branching ratio must be at least equal to the $\sqrt{n}$, 1.41, if the resistance to blood flow after a branching point is not to increase. The results of the present study show that resistance to flow in a single coronary artery is increased after a bifurcation. If all parallel branches are considered, however, the resistance will decrease when the overall cross-sectional area is sufficiently increased, such as at the level of the capillaries.[10] These considerations are based on the Poiseuille relation which assumes steady laminar flow in a rigid tube. A more precise analysis would involve the measurement of the impedance due to branching under conditions of pulsatile flow and would consider branches of variable size.

If the difference in coronary artery shear stress between normal and hypertrophied hearts is clinically significant, it may help explain the fact that chronic essential hypertension is a risk factor in the development of coronary artery disease. LV hypertrophy from chronic hypertension could cause increased blood flow velocity with a resulting increase in shear stress in the proximal coronary vessels, especially during periods of physiologic stress. In support of this theory, Wilens[6] reported a 7-fold increase in the prevalence of myocardial infarction when the size of the coronary arteries decreased to below 6 cm^2 of external surface area per 100 g of myocardium.

If hypertrophy itself is sufficient to cause a significant increase in the incidence of atheromatous lesions, then other disorders such as chronic valvular disease or dilated cardiomyopathy also would increase the risk of developing coronary artery disease. Since this association has not been made, the increase in blood pressure that accompanies chronic hypertension also may be important. An experiment that could have bearing on this discrepancy was carried out by Carew and Patel.[1] They evaluated the relative importance of circumferential tensile stress and shear stress in causing an increase in endothelial permeability to dye-tagged albumin in coronary arteries. These investigators found that increased circumferential tensile stress was more important than elevated shear stress. Elevated shear stress (>21.6 dynes/cm^2) became an important determinant of endothelial permeability only under conditions of high circumferential tensile stress. Hence, the combination of increased shear stress and increased circumferential tensile stress that accompanies the elevated arterial pressures in patients with LV hypertrophy due to hypertension theoretically could predispose to an increase in endothelial permeability and the subsequent development of atherosclerotic heart disease.

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Quantitative Detection of Regional Left Ventricular Contraction Abnormalities by 2-Dimensional Echocardiography

Comparison of Myocardial Thickening and Thinning And Endocardial Motion in a Canine Model

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Myocardial infarction (MI) was produced in 27 dogs by ligation of the left anterior descending coronary artery. Two-dimensional (2-D) echocardiograms were performed through the closed chest before and serially after coronary ligation, in both the acute and healing stages of MI. Two-dimensional echocardiographic studies performed before the animals were killed were analyzed for left ventricular (LV) contraction defects by 2 algorithms—1 involving systolic myocardial thickening and thinning and the other by determining the extent of endocardial motion to derive cavity area shrinkage. Using the thickening algorithm, myocardial dysfunction was detected in 93% of the animals with MI; with the area shrinkage method, contraction abnormalities were detected in 96% of the animals with MI. When the heart was divided from base to apex into 3 short-axis sections, the thickening algorithm showed a trend toward better identification of normal regions than the area shrinkage algorithm. However, in predicting the circumferential extent of MI, the thickening-thinning method of analysis showed no advantage over the endocardial motion method ($r = 0.77$, standard error of the estimate = 0.16 versus $r = 0.76$, standard error of the estimate [SEE] = 0.16; p = not significant [NS]).

These observations support the concept that either algorithm can be used effectively to detect the presence and quantify the circumferential extent of MI.

The use of 2-dimensional (2-D) echocardiography to detect regional left ventricular (LV) contraction abnormalities has been well documented.[1–4] Increasingly sophisticated technology has prompted a recent trend toward quantitative analysis of 2-D echocardiography. Nearly all of the studies dealing with the quantification of regional LV function have been based on analysis of LV endocardial motion.[5–11] However, evaluation of regional LV function by endocardial motion ignores the ability of echocardiography to assess transmural thickening and thinning, which is an intrinsic feature of myocardial performance independent of the swinging of the heart.[12–16] This attractive feature has led to a preference among echocardiographers for mural thickening analysis despite the fact that there has only been 1 study, performed in an open-chested canine model, which has demonstrated an advantage to thickening analysis as compared with measurement of endocardial motion by 2-D echocardiography.[17] In a closed-chest subject, particularly in the clinical setting, epicardial targets are not always detected with sufficient accuracy to allow thickening analysis. Hence, it becomes important to define in a model more analogous to the clinical situation just what is gained and lost in attempting to define regional contraction defects by each of these methods. The present study was designed to compare the relative merits of endocardial motion and mural thickening analyses in association with both acute and healing myocardial infarction (MI).

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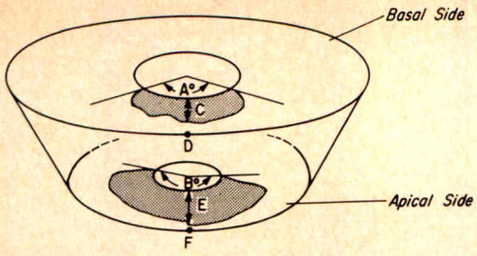
Methods

Healthy mongrel dogs weighing 15 to 25 kg were anesthetized with sodium pentobarbital (25 mg/kg, intravenously); 2-D echocardiographic examinations were performed through the chest wall with the animal in the right decubitus position.[18] Animals were selected for study on the basis of an initial



$$\text{Mean Circumferential Extent} = \frac{\frac{A^\circ + B^\circ}{2}}{360^\circ} \times 100\%$$

$$\text{Maximal Circumferential Extent} = \frac{B^\circ}{360^\circ} \times 100\%$$

$$\text{Maximal Transmural Extent} = \frac{E}{F} \times 100\%$$

FIGURE 1. Definitions of the extents of MI in a schematic LV pathologic specimen (bread-loaf slice). Area of MI is shown by **stippling.** A = the angle on the basal side of the pathologic slice which defines its circumferential extent of MI; B = angle on the slice's apical side which defines its circumferential extent of MI; C = maximal transmural thickness of the MI on the basal side of the slice; D = point used to measure myocardial thickness of the slice's basal side; E = the maximal transmural thickness of the MI on the slice's apical side; F = point used to measure the myocardial thickness of the slice's apical side.

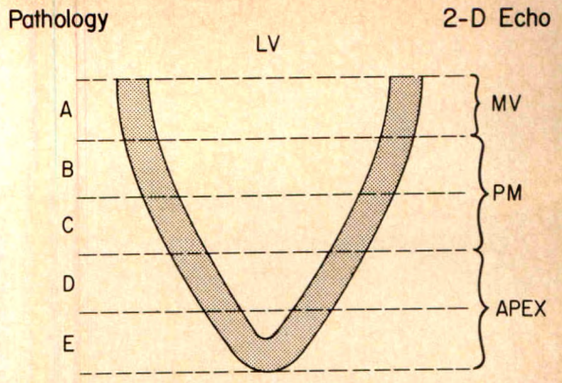


FIGURE 2. Relationship of the pathologic slices to the 2-D echocardiographic short-axis views. The left ventricle (LV) was imaged by 2-D echocardiography at 3 short-axis levels: mitral valve (MV), papillary muscles (PM), and cardiac apex (APEX). At pathologic examination, the isolated left ventricle was sliced in bread loaf fashion at 1 cm intervals—A, B, C, D, E, and so forth (see text for further explanation).

2-D echocardiographic examination which showed clear definition of LV epicardial and endocardial targets.

MI was produced through an open thoracotomy incision by ligation of the left anterior descending coronary artery. The chest was then closed and the animals were studied again by 2-D echocardiography before being killed. Animals were studied in 2 groups: an acute series in which they were killed 48 hours after coronary ligation, and a delayed series in which animals were killed periodically at intervals beyond 48 hours.

At postmortem, the heart was excised and cut into transverse, 1 cm thick sections from base to apex, parallel to the atrioventricular groove. These sections were then incubated for 15 minutes in triphenyl tetrazolium chloride (TTC) to assess size and location of the infarct; they were photographed and the normal and infarcted regions were traced on acetate sheets.[19,20]

From these pathologic tracings, the following indexes were determined for each slice: mean circumferential extent of MI, maximal circumferential extent of MI, and maximal transmural extent of MI as shown in Figure 1. The circumferential extent of MI on each side of each slice was measured as an angle, the vertex of which was located at the center of the LV cavity with rays directed tangentially along the edges of the infarcted area. The mean circumferential extent of MI for each slice was calculated as the average of the circumferential extent of MI measured on its basal and apical sides. The maximal circumferential extent of MI for each slice was defined as the greater circumferential percentage of MI on either its basal or apical side. The maximal transmural extent of MI was determined by the greater percentage of myocardial thickness that was infarcted on either the basal or apical side of each pathologic slice.

Since 2-D echocardiographic examinations were performed on a closed-chest canine model, in a manner analogous to clinical studies, it was impossible to obtain 2-D echocardiographic short-axis views that corresponded *exactly* to the thickness and number of the pathologic "bread-loaf" slices. Therefore, in order to compare the pathologic findings in the LV myocardium with the results obtained by 2-D echocardiographic examination, the pathologic slices were grouped by their anatomic landmarks in the following manner (Fig. 2). Section A, the pathologic specimen at the base of the heart, was related to the 2-D echocardiographic short-axis section which showed mitral valve elements. Pathologic sections B and C, which contained the papillary muscles, were related to short-axis echoes at the mid-left ventricle, in which the papillary muscles were visualized. The pathologic specimens D, E, and so forth were below the papillary muscles and were related to the lowest portion of the 2-D echocardiographic LV image, which did not show the papillary muscles. Thus, when comparing the circumferential extent of MI found at pathologic examination with the regional wall motion abnormality obtained by 2-D echocardiography, the papillary muscles' extent by pathologic examination was composed either of the mean of sections B and C (for mean circumferential extent) or the maximal extent found on either sections B and C (for maximal circumferential extent). In a similar fashion, we determined the mean and maximal circumferential extent of MI at the cardiac apex. The maximal transmural extent of MI was determined as the maximal percentage of myocardial thickness infarcted on either side of sections B and C for papillary muscles' extent, and on either side of slices D and E for the apical extent.

Image analysis was performed from studies recorded on a reel-to-reel video recorder (Panasonic NV3160) using ½-in videotape (Scotch 361). In all instances, outlines were traced from stop-frame images and were confirmed by playing through preceding and succeeding beats using both real-time and slow-motion playback. Cross-sectional images were traced from the video monitor onto clear acetate sheets. End-diastole was defined at the first deflection of the QRS complex, and end-systole was measured as the smallest ventricular cavity image during the last half of the T wave. These outlines were entered into a computer (PDP 11/05, Digital Equipment) by way of a light-pen digitizer (Electronics for Medicine) previously described (Fig. 3).[21] The outlines were analyzed as previously described by 2 different algorithms—thickening and cavity area shrinkage (Fig. 4)—for each of 8 octants at the mitral valve, papillary muscle, and apical cross-sectional levels.[16,21] In brief, the midpoint of the ventricular septum was

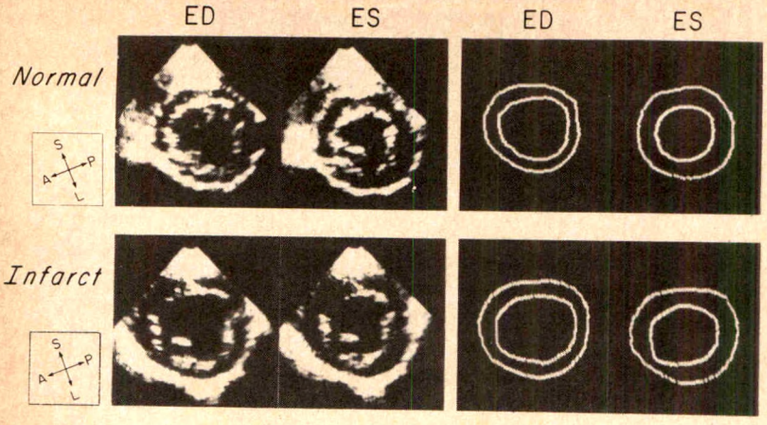


FIGURE 3. Two-dimensional echocardiograms at the level of the papillary muscles and their corresponding computer-generated epicardial and endocardial outlines. **Top left,** baseline (preligation) 2-D echocardiograms at end-diastole (ED) and at end-systole (ES). **Top right,** corresponding computer-generated outlines: ED (left); ES (right). **Bottom left,** 2-D echocardiography at ED and at ES 7 days after coronary ligation. **Bottom right,** their corresponding computer-generated outlines: ED (left); ES (right). A = anterior; L = lateral; P = posterior; S = septal.

defined as the point on the right ventricular-septal endocardial surface equidistant from the junctions of the right ventricle with the ventricular septum of LV free wall. Because of the lack of a right ventricular cavity at the cardiac apex, an equivalent point corresponding to the septal midpoint was defined. This point was placed in the same position on the circumference of the LV cavity as occurred with the septal midpoint in the immediately superior short-axis level, which was confirmed by scanning from the cardiac apex through the level of the papillary muscles. From the septal midpoint, an initial line was constructed to the lateral wall so as to divide the LV cavity into anterior and posterior halves of equal areas. From the midpoint of this line, the image was then subdivided at 45° angles into octants.

Twenty healthy dogs were used to define the normal range (mean ± 2 standard deviations) in each octant for both thickening and area shrinkage analyses. For the experimental group, an octant was considered abnormal if its contraction value was less than the lower limit of the normal range (mean − 2 standard deviations) of that octant. The circumferential extent of MI seen by 2-D echocardiography was defined as the number of abnormal octants in a short-axis view divided by 8 octants ×100%.

Previously in our laboratory, interobserver variability for the cavity area shrinkage method was extensively addressed and averaged 7.6%.[21] In a subsequent study, the intraobserver reproducibility of the myocardial thickening analysis in assessing infarct size showed a mean difference in paired observations of 4.9%.[16]

Statistical analyses were performed with a programmable Monroe 325 desk-top calculator. Sensitivity was defined as the number of 2-D echocardiographic short-axis views with abnormal contraction values which corresponded to infarcted pathologic cross-sections divided by the total number of infarcted pathologic cross-sections. Specificity was defined as the number of 2-D echocardiographic short-axis levels with normal contraction values which correspond to noninfarcted pathologic cross-sections divided by the total number of noninfarcted pathologic cross-sections. Accuracy was defined as (the number of 2-D echocardiographic short-axis sections with abnormal contraction values which corresponded to infarcted pathologic cross-sections plus the number of 2-D echocardiographic short-axis levels with normal contraction values which corresponded to noninfarcted pathologic cross-sections) divided by (the total number of pathologic cross-sections). Means, standard deviations, standard errors of the estimate, and correlation statistics were calculated using Monroe's Alpha 315 Univariate Statistics Pak and Regression Analysis Pak, respectively. Statistical significances were determined for proportions and standard errors of the estimates by the following tests: (1) the comparison of proportions in paired samples, and (2) a test of the equality of 2 variances, respectively.[22]

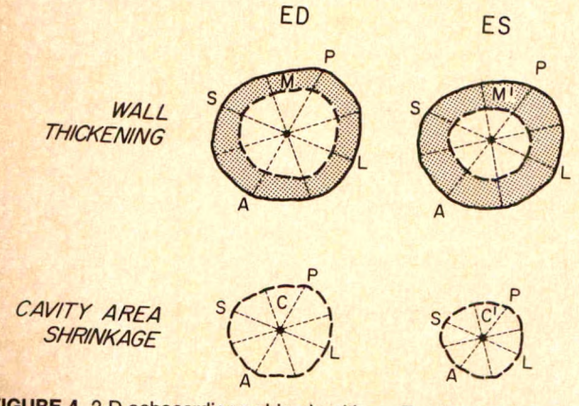


FIGURE 4. 2-D echocardiographic algorithms. Tracings of 2-D echocardiographic short-axis views were entered into a computer system that analyzed them both by the thickening method and by the cavity area shrinkage algorithm. Both algorithms utilize a floating axis format which rotates and translates the systolic outline so that the center point and the axes are superimposed upon the diastolic outline. Percent myocardial thickening in an octant is defined as $(M' - M) \div M \times 100$; percent cavity area shrinkage in an octant is defined as $(C - C') \div C \times 100$. **Continuous line,** epicardium; **heavy broken line,** endocardium; **thin broken line,** computer-generated axes; **blackened point,** computer-generated midpoint of S–L axis. A = anterior; C = LV cavity octant area at ED; C′ = LV cavity octant area at ES; ED = end-diastole; ES = end-systole, M = myocardial thickness at ED; M′ = myocardial thickness at ES; L = lateral; P = posterior; S = septal.

Results

A total of 27 dogs were studied: 14 were studied at 48 hours (acute series) and 13 were studied at intervals beyond 48 hours (evolving series). Of the 13 dogs in the evolving series, 2 were killed at 1 week, 2 at 2 weeks, 5 at 3 weeks, 3 at 6 weeks, and 1 at 8 weeks.

Pathologic examination: Of the 27 hearts, 21 were sliced into six 1-cm thick transverse sections. Four hearts were so small that they could only be sliced into five 1-cm thick sections; 2 were so large that they were sliced into seven 1-cm thick sections. In evaluating these pathologic sections, the most apical slice (the tip of the left ventricle) did not contain a cavity and as a result could not be compared with the 2-D echocardiographic

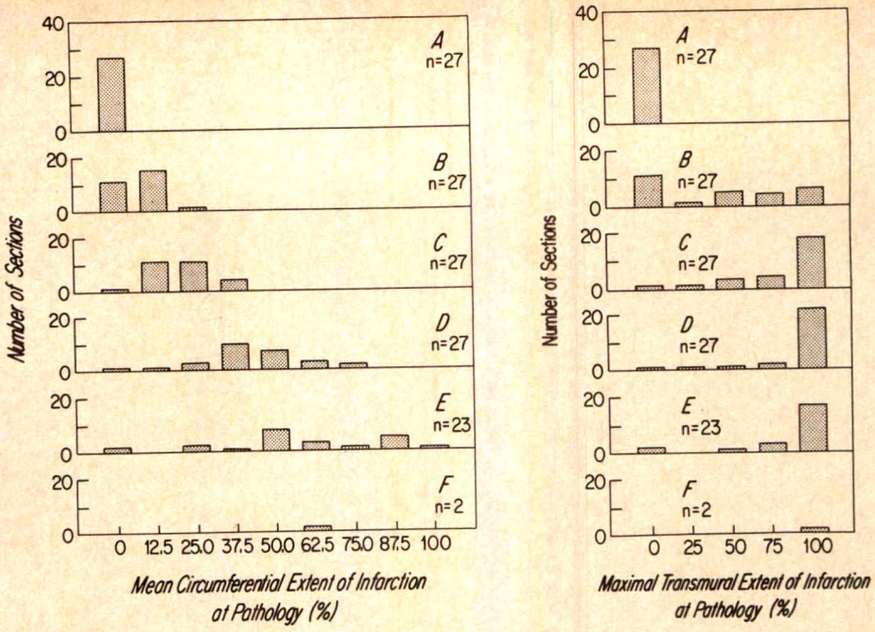


FIGURE 5. Left, Frequency distribution of mean circumferential extent of MI in the pathologic bread-loaf slices (calculated to the nearest 12.5%). Section A is the only slice that was totally free of myocardial damage in all the excised hearts. As the left ventricular apex (sections D, E, and F) was approached, the circumferential extent of MI was more heterogeneous. **Right,** frequency distribution of the maximal transmural extent of MI (calculated to the nearest 25%) found in the different pathologic segments. Section A was totally free from myocardial injury. As the left ventricular apex (sections D, E, and F) was approached, maximal transmural extent skewed toward 100%.

short-axis view of the LV apex. In most hearts, sections D and E were combined as described above. In the 4 hearts with only 5 slices, section D was equated to the cardiac apex. In the 2 hearts with 7 sections, slices D, E, and F were equated to the LV apex.

At postmortem examination, all excised hearts were found to have MI present in 1 or more of the "bread loaf" slices. Figure 5, left shows the frequency distribution of the mean *circumferential* extent of MI in the pathologic slices. In all 27 hearts, pathologic section A was found to be free of MI. In 1 of the excised hearts, both slices B and C were free of myocardial damage; in another, sections D and E were found to be free of MI. Therefore, after grouping the pathologic specimens to correspond to 2-D echocardiographic tomographic levels (see Methods and Figure 2), 52 of 54 combined slices below the level of section A had some degree of MI present; alternatively, 29 combined slices were free of infarction. As the LV apex (sections D, E, and F) was approached, the circumferential extent of MI became more heterogeneous.

Figure 5, right shows the frequency distribution of the maximal *transmural* extent of MI. Of these pathologic slices with MI (sections B to F), 28% had maximal transmural extent of MI of ≤50%. When the findings in these slices were combined for comparison with the 2-D echocardiographic short-axis views, only 6 of 52 (11.5%) had maximal transmural extent of MI of ≤50%. The maximal transmural extent of MI skews to the right (toward 100% transmural extent) as the LV apex (sections D, E, and F) was approached.

Two-dimensional echocardiographic examination: *Detecting and localizing the presence or absence of myocardial infarction:* Sensitivity was analyzed by (1) considering individual dogs, and (2) considering individual cross-sections. With the area shrinkage method, 26 of 27 dogs (96%) were assessed correctly; using the thickening-thinning algorithm, 25 of 27 dogs (93%) were assessed correctly (p = NS). In detecting MI at a particular cross-sectional level, the cavity area shrinkage algorithm identified 40 of 52 2-D echocardiographic short-axis sections (77%) correctly, and the thickening method identified 42 of 52 short-axis sections (81%) correctly (p = NS).

Since all dogs had MI present at pathologic examination, specificity could not be assessed for individual animals. However, specificity was evaluated on the 29 pathologic sections that were free of MI. Utilizing the cavity area shrinkage method, 24 of 29 2-D echocardiographic short-axis views (83%) had all octants within the normal contraction range; with the thickening algorithm, 29 of 29 2-D echocardiographic short-axis views (100%) had all octants within the normal contraction range (p = NS). Of the 232 octants from these 29 pathologic slices, the area shrinkage method correctly assessed 225 octants (97%); the thickening algorithm correctly identified all 232 octants (100%) ($p < 0.05$).

The accuracy of algorithms assessed both infarcted and noninfarcted regions; thus, comparing all the 2-D echocardiographic short-axis views with all pathological cross-sections, the accuracy of cavity area shrinkage analysis was 64 of 81 (79%) and that of the thickening-thinning method was 71 of 81 (88%) (p = NS).

Figure 6A shows the frequency distribution of pathologic sections with MI which were not identified by each method. Of those missed by the thickening al-

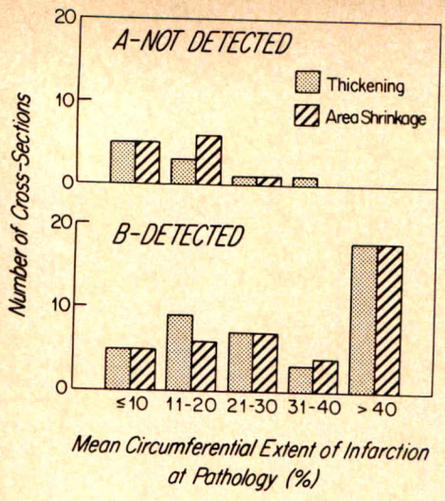


FIGURE 6. A, frequency distribution of the mean circumferential extent of MI at pathologic examinations *not detected* by 2-D echocardiographic algorithms. **B,** frequency distribution of mean circumferential extent of MI at pathologic examination detected by 2-D echocardiographic algorithm.

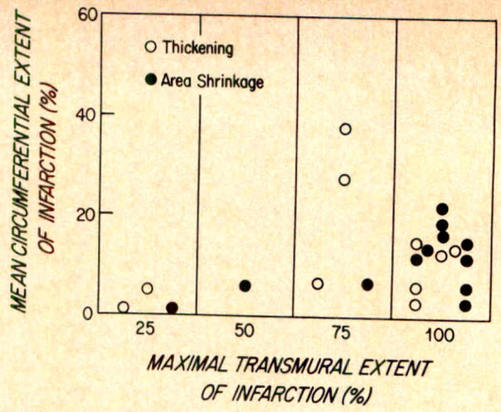


FIGURE 7. Plot of mean circumferential versus maximal transmural extent of MI for those infarcted 2-D echocardiographic short-axis levels *not detected* by 2-D echocardiographic algorithms. **Open circles,** the thickening method; **solid circles,** the area shrinkage algorithm.

ogirthm, 80% had mean circumferential extents of MI ≤20%. Of those not detected by the area shrinkage method, 92% had a mean circumferential extent of MI ≤20%. For each method, the areas of MI not detected were almost equally divided between the acute and the evolving series. Figure 6B shows the frequency distribution of infarcted cross-sections that were correctly identified by the 2-D echocardiographic algorithms.

For those areas of MI *not detected*, we evaluated the relationship of the circumferential to transmural extent of myocardial damage (Fig. 7). Though limited (usually <20%) in circumferential extent, the majority of the regions of MI which were not detected by either method were transmural.

Evaluating the circumferential extent of myocardial infarction: Figure 8 shows the relationship of the circumferential extent of MI determined by each 2-D echocardiographic method to the mean circumferential extent of MI at pathologic examination. With the area shrinkage algorithm, there was a more systematic overprediction by 2-D echocardiography of the circumferential extent of MI. The thickening analysis had a regression equation: Pathology = 0.72 2-D echocardiography + 0.08 (r = 0.77, SEE = 0.16). The regression equation for the relationship of mean circumferential extent of MI by pathology and the area shrinkage analysis was as follows: Pathology = 0.49 2-D echocardiography + 0.08 (r = 0.76, SEE = 0.16). These SEE pairs were not significantly different. When the maximal circumferential extent of MI by pathology was compared with the circumferential extent by each 2-D echocardiographic method, the correlation coefficients and SEE pairs were very similar to those for the above analysis (thickening: r = 0.75, SEE = 0.18; area shrinkage: r = 0.73, SEE = 0.19; p = NS).

Discussion

The problem of detecting and quantifying MI using ultrasonic methods is receiving increased attention as high quality, portable 2-D echocardiographic imaging units are progressively introduced into the critical care setting. Previous studies, in experimental animals, have utilized devices such as ultrasonic micrometer crystals,

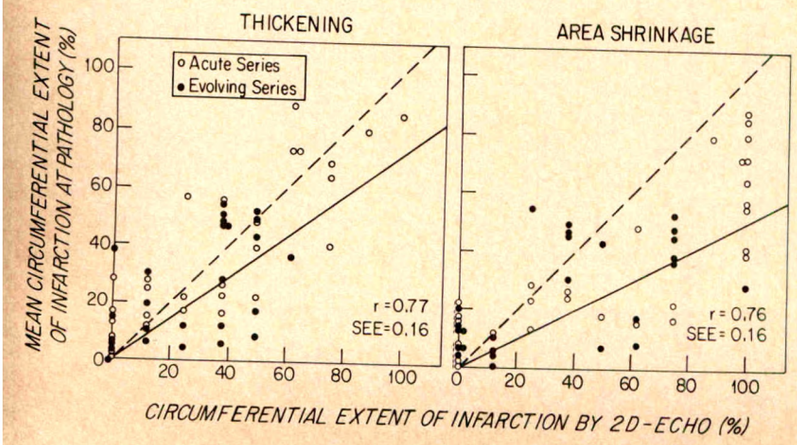


FIGURE 8. Plots of circumferential extent of MI: mean pathologic versus 2-dimensional echocardiographic (2-D echo). **Left,** thickening method. **Right,** area shrinkage method.

piezoresistive force gauges, and epicardial surface transducers to evaluate the regional wall motion changes associated with acute MI.[17,18,23–27] Although ultrasonic crystals can evaluate a precise site of dysfunction associated with MI and an epicardial surface transducer can match 2-D echocardiographic short-axis views with pathologic "bread-loaf" slices, these approaches are not directly applicable in a clinical setting. In a closed-chest model, the ultrasonic transducer is further away from the heart and the beam must penetrate greater amounts of tissue. Under these circumstances, information may be less accurate due to beam divergence and beam attenuation.

As increasingly sophisticated 2-D echocardiographic analysis equipment emerges, particularly computerized digital acquisition and automated edge detection techniques,[28] there arises a need to establish the attributes and limitations of systematically developed algorithms for measurement. In this study, LV cavity area shrinkage and myocardial thickening and thinning were evaluated because these 2 algorithms have been used most extensively in independent studies.

With some qualifications, our results extend to the closed-chest animal recent studies in an open-chest model. Lieberman et al[17] compared an endocardial motion algorithm and a myocardial thickening algorithm with the pathologic extent of MI. They reported that the thickening-thinning algorithm was superior because it produced less overlap between the remote normal zones, normal zones adjacent to areas of MI, and the infarct zones. Our results suggest that while this is indeed the case, endocardial motion is still a valid means of identifying some degree of MI in the injured whole heart.

In this study, there were a number of small circumferentially infarcted zones that were not detected by either method. Since our computer analysis divided each short-axis view into octants, infarcts <12.5% of the circumference might not, theoretically, be detected. Thus, a system which subdivides short-axis views further might improve sensitivity. Besides the circumferential extent of MI, the transmural extent must be considered. Since there were very few cross sections in this study with transmural extents of MI <50%, nothing conclusive can be inferred from our data about the degree of systolic thickening and thinning in relation to transmural extent of MI. The detection and quantification of subendocardial MI would be studied more properly in a model in which most zones of myocardial damage were <50% of the mural thickness.

The problem of assessing infarct size is more complex than just the overprediction or underprediction of the area of MI. Wall motion or contraction abnormalities do not necessarily reflect the extent of myocardial necrosis. Nieminen et al[16] showed that, in a canine model 2 to 48 hours after coronary artery ligation, 2-D echocardiographic estimation of infarct size from wall motion abnormalities decreased. Thus, there is a dynamic aspect to the evolution of wall motion abnormalities, particularly early after MI. While this may be due, in part, to slow evolution of histologic changes associated with MI and developing collateral blood flow which promotes some functional recovery, a system which will simultaneously integrate myocardial contraction defects with the assessment of tissue characteristics is needed to enhance detection of tissue necrosis.

In conclusion, the mechanical and computerized approach used in this study is a valid alternative to the subjective visual inspection techniques successfully used by others.[1,3–5] Our results indicate that (1) a statistically significant difference in the detection of the presence of MI either by the cavity area shrinkage algorithm or by the thickening-thinning algorithm could not be demonstrated in this series; (2) both algorithms *failed to detect* some areas of MI, but these segments were were usually limited in the circumferential extent, though not necessarily limited in the transmural extent; (3) when the cross-sections *free* of MI were evaluated by the 2-D echocardiographic algorithms, there was a trend toward better identification with thickening than with the area shrinkage algorithm, but only when specificity was evaluated by subdividing into octants did a statistically significant difference emerge; and (4) when used to quantify the circumferential extent of MI, although the thickening method tended to overestimate infarct size less, both algorithms had nearly identical correlation coefficients and estimating errors.

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Pharmacologically Induced Changes in Wall Thickening Dynamics and Mid-Ventricular Volumes in Dogs Assessed by Prospectively Gated Computed Tomography

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With the technical assistance of STEPHEN A. LONG

Assessment of regional wall thickening dynamics is important for monitoring the response of normal and ischemic myocardium to pharmacologic interventions. Because regional wall thickness can be measured on computed tomographic (CT) scans of the heart, the ability of electrocardiogram-gated computed tomography to determine the effects of pharmacologic agents on global and segmental left ventricular (LV) function was assessed. Eight conditioned dogs were studied at a control state and during drug-induced changes in contractility and loading conditions brought about by the use of isoproterenol (0.15 μg/kg/min), phenylephrine (0.3 μg/kg/min), and verapamil (0.2 mg/kg infused over 10 minutes). Ten contrast-enhanced CT slices (1 cm thick) at the same mid-LV level were reconstructed for each 10% of the R-R interval throughout an average cardiac cycle using prospectively gated CT scans. End-diastolic and end-systolic frames were selected and analyzed for the following: septal, apical, and lateral wall thickness, percent wall thickening, end-diastolic and end-systolic mid-LV volume, and percent change in mid-LV volume.

During control, end-diastolic and end-systolic LV wall thicknesses (in millimeters) were 12 ± 2 and 15 ± 2 for the septal wall, 8 ± 1 and 11 ± 2 for the apical wall, and 10 ± 1 and 12 ± 1 for the lateral wall, respectively. The percent thickening in these respective segments was 24 ± 8, 36 ± 10, and 28 ± 13. The control end-diastolic and end-systolic mid-LV volumes were 16 ± 3 and 12 ± 3 ml, resulting in a percent change of 27 ± 7%. Phenylephrine induced significant thinning of the walls and impairment of systolic thickening, whereas isoproterenol induced opposite effects. Verapamil produced a significant decrease in mean blood pressure (123 ± 9 versus 99 ± 23 mm Hg, $p < 0.025$), but end-diastolic wall thicknesses were mildly thicker or showed no change and end-systolic wall thicknesses showed no change compared with those in the control state. Similarly, mid-LV volumes and percent change in mid-LV volumes were not different from those during control. Thus, electrocardiogram-gated computed tomography can be used to assess the effects of pharmacologic interventions on global and segmental LV function.

Dynamic features of wall thickening are important in evaluating the mechanical performance of the left ventricle.[1–4] Numerous techniques are available for the quantitative measurement of this important parameter,[5–15] but only a few are noninvasive or semiinvasive and hence potentially of widespread clinical use in man.[16–18] Noninvasive assessment of regional wall thickening dynamics is important for monitoring and comparing the regional myocardial response to interventions in coronary heart disease. The currently available cross-sectional imaging techniques, echocardiography and computed tomography, can be used to measure left ventricular (LV) wall thickness throughout the cardiac cycle,[19–26] but the use of computed tomography in assessing the dynamic effects of pharmacologic agents has not been evaluated. This study determines the use of prospectively gated computed tomography in assessing directional changes in wall thickening dynamics in dogs. We sought to define the effects of alterations in contractile state and loading conditions on global and regional function as produced by infusions of isoproterenol, phenylephrine, and verapamil.

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Methods

Protocol: Eight conditioned dogs weighing 26 ± 5 kg (mean ± standard deviation) were premedicated with morphine sulfate (3.6 ± 0.6 mg/kg), anesthetized with sodium pento-

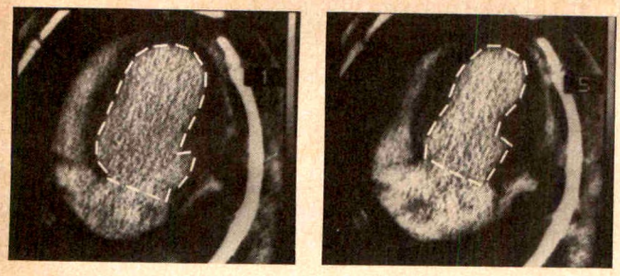

FIGURE 1. Mid-ventricular endocardial outlines. Planimetered areas at end-diastole (**left**) and end-systole (**right**) are demonstrated.

barbital (22 ± 5 mg/kg), and paralyzed with succinylcholine (1.7 ± 0.3 mg/kg). Respirations were maintained at a rate of 16 breaths/min with a Harvard respirator. A femoral artery cannula was connected to a Statham P23dB pressure transducer. Two separate peripheral veins were cannulated for infusion of drugs and contrast material.

Renografin®-76 (sodium meglumine diatrizoate) was infused with a Harvard infusion pump at 6.1 ml/min for 10 minutes and then at 4.4 ml/min for the duration of the experiment. A control scan, described subsequently, was taken once the heart rate and blood pressure were stable after initiation of the contrast infusion. Subsequently, scans were taken during steady-state administration of phenylephrine (0.3 μg/kg/min) and isoproterenol (0.15 μg/kg/min), and 5 to 10 minutes after verapamil administration (0.2 mg/kg given over a 10-minute period). All scans were taken once the heart rate and blood pressure had attained a new, stable level which did not change during the scan acquisitions. The dogs were allowed ample time to attain control heart rate and blood pressure after cessation of each intervention and before initiation of subsequent drug infusions, so that no residual drug effects were present.

Imaging technique: Imaging was performed using a 2020 Technicare scanner with a prototype prospective gating system.[26] Gated computed tomographic scans were obtained by acquiring X-ray data in relation to a preselected fraction of the electrocardiographic R-R interval width, called the biologic window. The biologic window was set at 10% of the R-R interval in this study. The prospective gating technique programmed sequential scans, one 2-second scan each 7 seconds, to obtain all 360° of data for each 10% fraction of the cardiac cycle. A prospective monitoring program updated the display immediately after each scan to show the gaps still present in the angular (360°) X-ray data for 1 biologic window. After the initial scan the prospective gating system sets the launching of the X-ray tube at the appropriate time to position the next preselected portion of the R-R interval in the largest gap in the angular data. Six to 8 scans were required to obtain a full complement of gated angular data for the preselected biologic window. Because each scan actually collected data during the entire 360° rotation of the gantry, when the biologic window was filled, it was possible to reconstruct multiple images (10 per R-R interval in this study) all having the same preselected interval width depicting the cardiac cycle from end-diastole to end-diastole. Unlike retrospective gating, prospective gating minimizes the time and the number of scans necessary to image the preselected fraction of the R-R interval width with small or no gaps in the angular data. Because each biologic window was 10% of the R-R interval and the animals sustained a heart rate of 90 to 190 beats/min during scanning, the end-diastolic and end-systolic gating intervals were 32 to 67 ms in duration.

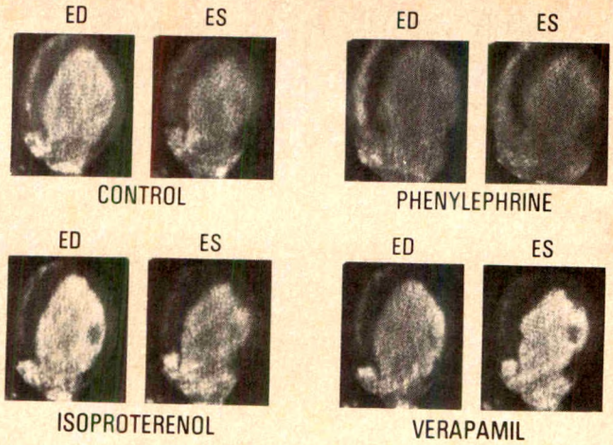

FIGURE 2. End-diastolic (ED) and end-systolic (ES) frames obtained during control state and during pharmacologic interventions, demonstrating changes in wall thickness and mid-LV volume.

Gated scans were performed over the mid-LV level during held inspiration. The scans were acquired during a steady state of contrast infusion, while heart rate and blood pressure remained stable. The scanning technique was set at 120 kVp, 100 mA, 10 mm slice thickness, and a 25 cm scanning circle. The approximated midline radiation dose for a gated series of scans (approximately 8 scans) was 1 to 2 rads in a precisely collimated X-ray beam of 1 cm thickness.

Each of the 10 images, comprising a single cardiac cycle, was displayed on the TV monitor using a 512 × 512 image matrix. A 12.5 × 12.5 cm square was placed over the heart and magnified to fill the entire 512 × 512 matrix. Each pixel thus represented 0.24 × 0.24 mm in real life. A variable region of interest was drawn over the LV wall and the average Hounsfield units (HU) and standard deviation were obtained. The mean Hounsfield units of the LV wall measured approximately 60, whereas the enhanced LV lumen measured 175, thus providing a clear edge. The window was set at approximately 500 HU such that each 8 HU was compressed into 1 gray level. The center was set at the average Hounsfield unit measured over the LV wall. The window and center were then maintained constant for the entire series.

Measurements: The 10 frames at the mid-LV level representing 10% portions of the average heartbeat were displayed along with reference distance markers, and the end-diastolic and end-systolic frames were selected. The end-diastolic figure was the initial frame which corresponded to the 10% interval encompassing the QRS complex, whereas the end-systolic frame was identified as the one with the smallest luminal area. End-diastolic and end-systolic areas were planimetered (Fig. 1) and converted into mid-LV volumes in cubic centimeters, each slice being 1 cm thick. The percent change in mid-LV volume was calculated as the difference between end-diastolic and end-systolic volume divided by end-diastolic volume and expressed as a percentage, referred to as the "mid-LV ejection fraction."

LV wall thickness was measured by placing a movable cursor, available as a display function, across the LV wall. The measurement was given automatically by the display program. The septum was measured directly across from the papillary muscle identified on the lateral LV wall. The anterior wall was measured at the apex of the LV lumen. The lateral wall was measured just below the papillary muscle. The same position was measured on the end-diastolic and end-systolic images (Fig. 2). The percent thickening was calculated as the differ-

TABLE I Summary of Study Parameters

	Control	Phenylephrine	Isoproterenol	Verapamil
Heart rate (beats/min)	137 ± 25	118 ± 26*	163 ± 28†	138 ± 19
Mean blood pressure (mm Hg)	123 ± 9	186 ± 16‡	111 ± 16§	99 ± 23§
Systolic blood pressure (mm Hg)	156 ± 24	245 ± 35‡	150 ± 30	139 ± 30¶
Wall thickness (mm)				
(1) End-diastolic				
Mid-septum	11.9 ± 1.6	10.4 ± 1.8‡	13.1 ± 2.0¶	12.8 ± 2.1§
Apex	8.3 ± 0.7	7.5 ± 1.1§	10.0 ± 2.9¶	9.1 ± 1.4¶
Lateral	9.6 ± 1.4	8.1 ± 0.6§	10.8 ± 1.8	10.0 ± 1.4
(2) End-systolic				
Mid-septum	14.8 ± 2.1	11.6 ± 2.1‡	17.6 ± 3.0‡	15.8 ± 3.3
Apex	11.3 ± 1.7	9.4 ± 1.4‡	16.6 ± 5.7§	12.1 ± 1.6
Lateral	12.3 ± 1.5	9.6 ± 1.1‡	15.1 ± 3.7¶	11.9 ± 1.9
Percent thickening				
Mid-septum	24.3 ± 7.9	12.0 ± 5.6‡	32.9 ± 8.7§	23.4 ± 13.9
Apex	36.0 ± 10.5	25.3 ± 8.2§	66.4 ± 27.3§	34.6 ± 19.8
Lateral	28.3 ± 13.2	18.6 ± 9.3¶	38.4 ± 17.2¶	18.9 ± 11.8¶
Mid-ventricular volumes (ml)				
(1) End-diastolic	16.0 ± 3.1	19.7 ± 4.1‡	12.9 ± 4.4†	16.5 ± 3.4
(2) End-systolic	11.7 ± 3.0	15.0 ± 3.0‡	7.9 ± 3.8‡	11.8 ± 3.2
Mid-ventricular ejection fraction (%)	27.4 ± 6.9	23.4 ± 3.2	40.6 ± 14.7§	29.1 ± 6.4

* $p < 0.01$ compared with control values.
† $p < 0.005$ compared with control values.
‡ $p < 0.001$ compared with control values.
§ $p < 0.025$ compared with control values.
¶ $p < 0.05$ compared with control values.
Values given are means ± 1 standard deviation.

ence between end-systolic and end-diastolic thickness divided by end-diastolic thickness and expressed as a percentage.

Wall thicknesses and mid-LV volumes were calculated by 1 observer on 2 occasions separated by >3 weeks and by a second independent observer. Data were analyzed by the paired Student's *t* test. All thickness values are given in millimeters.

Results

The results of the study parameters are summarized in Table I and Figures 3 and 4. Phenylephrine induced predictable increases in blood pressure and a decrease in heart rate. These changes were associated with significant thinning of the LV walls at both end-diastole and end-systole and a decrease in percent thickening from 24 ± 8 to 12 ± 6 ($p < 0.001$) in the septum, from 36 ± 10 to 25 ± 8 ($p < 0.025$) in the apex, and from 28 ± 13 to 19 ± 9 ($p < 0.05$) in the lateral wall. Mid-LV volumes increased significantly as well, but although the mid-LV ejection fraction decreased modestly, the change from control was not statistically significant (27 ± 7 versus 23 ± 3%, p not significant [NS]).

Isoproterenol produced characteristic increases in heart rate and a decrease in mean blood pressure. Wall thicknesses and percent thickening increased substantially; however, the increased thickness of the lateral wall at end-diastole was not quite statistically significant (11 ± 2 versus 10 ± 1 mm at control, p = NS). Percent thickening increased from 24 ± 8 to 33 ± 9 ($p < 0.001$) in the septal wall, from 36 ± 10 to 66 ± 27 ($p < 0.025$) in the apex, and from 28 ± 13 to 38 ± 17 ($p < 0.05$) in the lateral wall.

Verapamil caused a decrease in systemic pressure without any significant change in heart rate compared with the control value. Although the septal and apical end-diastolic wall thickness was slightly thicker than that of the control, the lateral wall thickness at end-diastole was not statistically different from that of the control. Percent thickening for each segment was: septum, 23 ± 13 (p = NS versus control); apex, 35 ± 20 (p = NS versus control); lateral, 11 ± 12 ($p < 0.05$ versus control). Thus, despite the decrease in blood pressure, and with comparable heart rates, systolic thickening was not enhanced and was compatible with an overall impairment of systolic function. In fact, impaired systolic function was detected in the lateral wall. This change in systolic function was also reflected by the LV volumes; that is, despite the substantial decrease in afterload, the end-diastolic and end-systolic volume as well as the mid-LV ejection fraction were not different from the control.

The intraobserver variability was as follows: wall thickness, ±1.2 mm (±10%), range −1 to +2 mm; LV volume, ±0.6 ml (±3%), range −0.6 to +1.4 ml. The interobserver variability was: wall thickness, ±1.0 mm (±9.2%), range −2 to +2 mm; LV volume ±0.5 ml (±5%), range −1.0 to +1.6 ml.

Discussion

This study demonstrates that gated computed tomography of an intact canine model can be used to detect changes in segmental wall thickening dynamics and cross-sectional (global) LV function in response to pharmacologic interventions. The directional changes in response to isoproterenol and phenylephrine are in close agreement with the results from other investigators using invasive sonomicrometer techniques,[3] and the percent thickening in the control state (range of means 24 to 36% in all segments) agrees with results obtained with a variety of other techniques.[3,5,14,18,21,27,28] Furthermore, the present results were obtained in a relatively noninvasive fashion without limitations on the number of segments that could potentially be analyzed

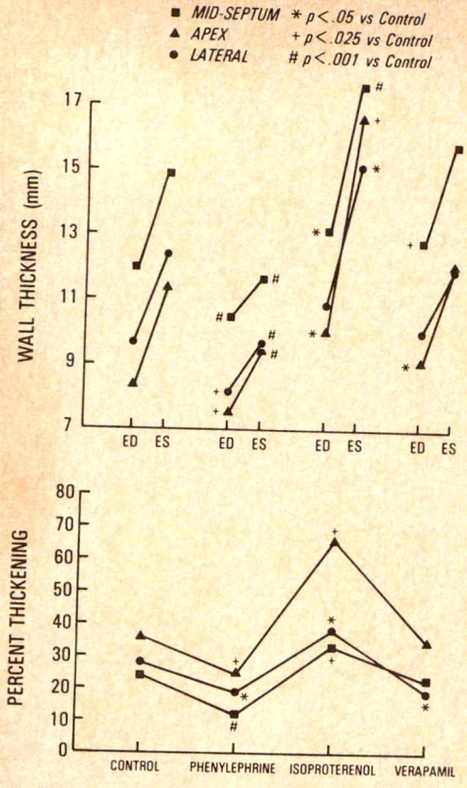

FIGURE 3. Computed tomographic wall thickening dynamics with pharmacologic interventions. ED = end-diastole; ES = end-systole.

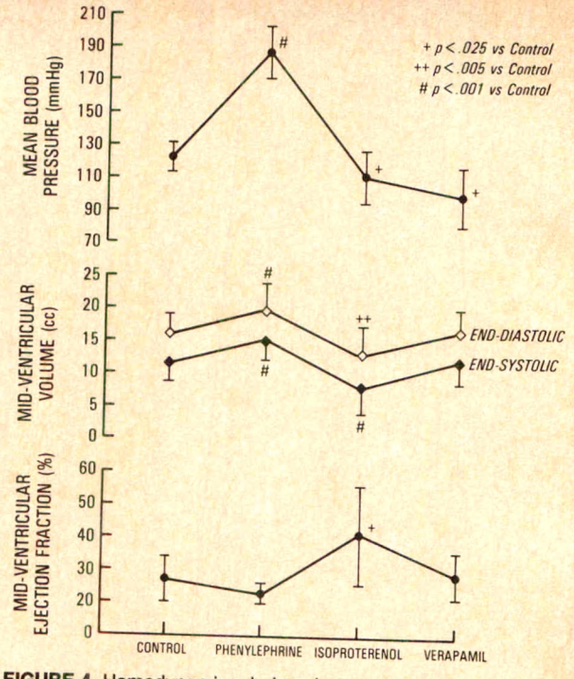

FIGURE 4. Hemodynamics during pharmacologic interventions.

and with the additional ability to assess global function.

Inotropic stimulation of isoproterenol induced a predictable increase in heart rate and a slight decrease in blood pressure in association with increased wall thickness and percent segmental thickening as well as a decrease in LV volume and an increase in mid-LV ejection fraction. Similarly, the known effects of phenylephrine were readily detected, that is, an increase in blood pressure and concomitant reflex bradycardia in conjunction with LV dilatation and wall thinning, and a depression in global and regional systolic function.

Verapamil is a slow channel antagonist with more complex properties than isoproterenol or phenylephrine. It simultaneously causes peripheral vasodilation and depression of myocardial contractility as well as inhibition of the slow response tissues of the sinoatrial and atrioventricular nodes.[29,30] The depression of contractility is largely offset both experimentally and clinically by the reduction in impedance to ventricular emptying and reflex sympathetic activation.[31,32] These effects were also demonstrated in the present study. In particular, although blood pressure decreased, there was little reflex tachycardia because of inhibition of sinoatrial nodal function. In the presence of this reduced afterload, systolic wall thickening remained the same or deteriorated, and the mid-LV end-diastolic volume and ejection fraction showed no change when compared with the control. This finding is in keeping with a depression of the contractile state induced by verapamil.[29–33]

There is a paucity of reports regarding the use of gated computed tomography to assess myocardial wall thickness, and there are no reports that assess its ability to study changes in LV wall thickening dynamics in response to pharmacologic interventions. Skioldebrand et al[19] showed that septal wall thickness measured by nongated computed tomography demonstrated an excellent correlation with autopsy measurements in dogs, although there was a consistent 10 to 20% underestimation of the actual thickness. They were able to detect significant differences in wall thickness in normal animals compared with those with aortic coarctation. Lackner and Thurn,[34] using gated tomography in man, demonstrated a decreased thickness of the ventricular wall in ischemic heart disease and an increase in aortic stenosis. More recently, Mattrey and Higgins[26] demonstrated changes in canine wall thickening dynamics in response to ischemia that could be shown with gated computed tomography and that were corroborated by implanted sonomicrometers.

Several current limitations of gated computed tomography merit discussion. Imaging requires the cessation of respiration and this time interval will depend on the desired number of images per R-R interval as well as the intrinsic heart rate. Imaging time in this canine model was <50 seconds but would be longer in human subjects with slower heart rates, and this would also entail a higher radiation exposure. In addition, a single, mid-LV image provides limitations in measuring true, global ejection fraction. Technical advances will largely eliminate these problems.[35] Contrast enhancement with ionic contrast material was used in this study

in large volumes primarily because of the length of the study. Clinically, doses of contrast material would be smaller with less protracted investigations in human subjects; in addition, newer nonionic contrast agents may prove more acceptable.[36–38]

The inter- and intraobserver variability of the measurements in this study were quite good and compare favorably with echocardiographic techniques even at this early stage of technical development.[39–41] We also previously showed small variability in sequential analysis of cardiac chamber function (end-diastolic and end-systolic volume as well as ejection fraction) when sequential imaging is performed.[42] However, imaging with computed tomography is not affected by lung disease, pericadial effusion, absence of an adequate interspace window, or variable transducer positioning which are all problems with echocardiography. Nevertheless, both of these 2-dimensional imaging techniques are prone to errors in determining absolute wall thickness at specific levels because of the complex nature of cardiac motion outside the plane being imaged.

Measurements of apical and lateral wall thickness in this study depend on detection of the epicardial surface at the heart-lung interface. Skioldebrand et al,[43] in assessing myocardial mass, demonstrated that the potential source of measuring error at this interface is very small. Relative changes in systolic wall thickening should be unaffected by this small error because this potential effect will be similar in both the end-diastolic and the end-systolic frames.

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Coronary Blood Flow During the Development and Regression of Left Ventricular Hypertrophy in Renovascular Hypertensive Rats

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Left ventricular (LV) coronary flow (CF) was determined by left atrial injection of microspheres in conscious rats during the development and after the reversal of LV hypertrophy in 2-kidney, 1-clip Goldblatt hypertension. Two groups of untreated renal hypertensive rats (RHR) were studied, the first (RHR_1, n = 17) at 10 weeks and the second (RHR_2, n = 9) at 24 weeks after clipping. Beginning 9 weeks after clipping, 2 other groups were treated either with captopril (40 to 60 mg/kg/day) in drinking water (RHR-C, n = 8) or left nephrectomy (RHR-N, n = 9) and followed for 15 weeks. Sham-operated animals followed for similar periods of time served as controls (Sham-1, n = 12, as a control for RHR_1, and Sham-2, n = 11, as a control for RHR_2). In all groups, LV mass increased or decreased in close correlation with changes in arterial blood pressure, and minimal total LV coronary resistance remained unchanged. The development of hypertrophy was associated with a tendency toward reduction in CF reserve (defined as maximal CF/unit mass); this flow reserve was restored with reversal of hypertrophy. The importance of the relation between pressure and LV mass as a determinant of CF reserve was investigated in a second study in which this relation was changed by altering the periods of captopril therapy; in these cases, CF reserve correlated significantly with the ratio of arterial pressure to LV mass ($r = 0.76$, n = 12, $p < 0.01$). The results suggest that maintenance of CF reserve in LV hypertrophy depends on an appropriate balance between arterial pressure and LV mass, and might be disturbed by antihypertensive therapy that leaves LV hypertrophy unchanged.

Most studies of left ventricular (LV) hypertrophy report that coronary flow (CF) per unit of LV mass is normal at rest,[1–6] although some investigators note either increased[7–10] or decreased[11–13] values. However, measurements of resting CF are of limited value in determining whether hypertrophied ventricles are at increased risk of ischemia. Resting myocardial perfusion is generally autoregulated according to metabolic needs.[14] Therefore, more fruitful as regards the potential risk of ischemia in cardiac hypertrophy is the concept of CF reserve. This concept describes the ability of the coronary circulation to augment flow and therefore to maintain an adequate metabolic supply when presented with increased myocardial requirements. CF reserve determined after maximal vasodilation, induced either pharmacologically or by exercise, usually remains within the normal range in pressure-overload hypertrophy[3,4,15,16] unless the latter is excessive.[10] However, CF in LV hypertrophy may be diminished in the subendocardial layers.[6,14,17]

In contrast to these many studies of developing or established LV hypertrophy, there have been few reports on myocardial perfusion after reversal of cardiac hypertrophy. Because chronic myocardial ischemia might be an aggravating factor for heart failure in cardiac hypertrophy, any information on the possibility of reversing potential coronary abnormalities with therapeutic intervention is of great interest. Therefore, these studies were designed to determine possible alterations in CF after reversal of LV hypertrophy as well as in situations in which blood pressure and LV mass are dissociated by therapeutic manipulations. This second step was designed because we have previously shown that some antihypertensive medications may control arterial pressure without reversing cardiac hypertrophy.[18–20]

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Methods

Male Sprague-Dawley rats (Hilltop Laboratory) were used in all studies; they were housed 2 to 3 in a cage, fed a standard rat chow (Purina Chow), given water at will, and handled in the same way for weekly blood pressure determinations.

Coronary Blood Flow Measurements

LVCF was measured under resting conditions and after coronary dilation by carbochrome in conscious unrestrained rats using left atrial injection of radioactive microspheres, as

described in detail previously.[21] A left atrial catheter was positioned under adequate anesthesia at least 72 hours before measurement of CF. After this surgical procedure, the rats were placed in separate cages and allowed to recover for 3 to 6 days. During this period, they were trained to sit quietly on small boxes so that subsequent measurements were made in conscious unrestrained animals. Details of the procedure and the accuracy of CF determination by this method have been reported previously.[21]

Approximately 12 hours before CF determination, the right femoral artery was cannulated with the rat under ether anesthesia and the catheter was advanced about 3.5 cm into the aorta to below the level of the renal arteries. On the day of the measurement the rats were placed on top of their boxes, where they sat quietly, and the femoral catheter was connected to a Micron MP-15 transducer for blood pressure recording. The first injection of microspheres was given 45 to 60 minutes later, after both blood pressure and heart rate had stabilized.

Preparation and injection of microspheres: Radioactive microspheres (diameter 15 μm), labeled with either strontium-85 or cerium-141, were suspended in a 70% glucose solution (with 0.05% Tween® 80), whose specific gravity (1.3) was equal to that of the microspheres. This solution was shown in preliminary experiments to have no significant effects on either blood pressure or heart rate in conscious rats. After mechanical and ultrasonic agitation for 10 minutes, approximately 60,000 to 65,000 microspheres were withdrawn in PE-50 tubing; the tubing was then sealed and counted for 1 minute before being connected to the left atrial catheter.

Just before the injection, the femoral catheter was connected to a constant rate withdrawal pump. The microspheres were injected over a 10-second period and the tubing was flushed with 0.2 ml of saline solution in 15 seconds. Starting 10 seconds before the injection, blood was withdrawn for 70 to 75 seconds through the femoral catheter at a constant rate of 1.03 ml/min. After the first microsphere injection, coronary vasodilation was induced by 6 mg/kg of carbochrome[22] infused at a constant rate of 0.17 mg/min through the left atrial catheter. Forty minutes after the beginning of the infusion, a second set of microspheres with a different radioisotope label was injected in exactly the same way. Blood pressure and heart rate (from the pressure tracings) were recorded before and after each injection and just before and at the end of the carbochrome infusion.

At the end of the experiment, the rats were sacrificed with an overdose of pentobarbital sodium. The heart was removed rapidly and cleaned of fat and fibrous tissue. After the proper location of the left atrial catheter was confirmed in all cases, the right ventricular free wall was peeled away, leaving the LV free wall plus the septum as 1 piece which will subsequently be referred to as "left ventricle." This piece was placed in a separate plastic vial, weighed, and counted for 5 minutes in a gamma-well counter at the same time as the blood was withdrawn from the femoral catheter (reference sample).

Calculation of blood flow: Blood flows were computed from the radioactivity in each sample and in the reference sample, according to standard formulas.[23] CF was expressed in both absolute (ml/m) and relative terms (ml/min/100 g of wet tissue). Relative LV coronary vascular resistance was obtained by dividing the mean aortic pressure by LVCF, and expressed in millimeters of mercury per milliliter per minute per 100 grams. Total LV coronary resistance was similarly computed using total LVCF and results were normalized for body weight; this normalization had been proposed by O'Keefe et al,[4] and its value was confirmed by our own experience. In 56 rats with a wide spectrum of LV mass, we found a significant linear correlation between total heart conductance and body weight ($r = 0.59$, $p < 0.001$).

Experimental Protocols

Study 1: Development and reversal of LV hypertrophy: *Preparation of 2-kidney, 1-clip Goldblatt hypertensive and sham-operated rats:* two-kidney, 1-clip renal hypertension was induced in rats weighing 175 to 200 g by placing a silver clip (0.2 mm) on the left renal artery with the rat under ether anesthesia; the right kidney was left untouched. Blood pressure was measured at weekly intervals by an indirect tail cuff method. The pressure increased in approximately 60% of the clipped rats, but only rats with blood pressure consistently >170 mm Hg were used in this study. All sham-operated rats remained normotensive.

Treatment of hypertension and reversal of cardiac hypertrophy: Nine weeks after clipping, the renal hypertensive rats were divided at random into 2 groups. The first (RHR-C, n = 8) was given captopril in drinking water at an initial dose of 30 mg/kg/day. This dosage was gradually increased to 40 to 60 mg/kg/day to maintain blood pressure levels near normal (<140 mm Hg). The second group (RHR-N, n = 9) underwent left nephrectomy under ether anesthesia at the same time that captopril was begun in the first group (that is, after 9 weeks of hypertension). Both groups were followed up 15 weeks before determination of CF and LV mass (24 weeks after renal arterial clipping). Two other groups of hypertensive rats were left untreated and studied, 1 at 10 weeks (RHR_1, n = 17) and the other at 24 weeks after induction of hypertension (RHR_2, n = 9). Sham-operated untreated rats were followed up exactly the same way as the hypertensive rats and for the same period of time; 1 group was studied after 10 weeks of follow-up (Sh_1, n = 12, corresponding to RHR_1) and the other after 24 weeks (Sh_2, n = 11, corresponding to RHR_2 and to the 2 groups of treated rats, RHR-C and RHR-N).

Study 2: Dissociation of arterial pressure from changes in LV mass: Hypertensive and sham-operated rats were prepared and treated as previously described, but the duration of the therapeutic periods was modified in an attempt to alter the relation between arterial pressure and LV mass. A first group of RHR (group RHRA, n = 7) was given captopril (60 to 80 mg/kg/day) for only 1 week so that blood pressure was normalized but no time was given for reversal of LV hypertrophy. A second group of RHR (group RHRB, n = 5) was treated with captopril for 14 to 15 weeks to induce reversal of LV hypertrophy as previously demonstrated[24]; the drug was then discontinued 9 to 12 days before microsphere determination to allow the blood pressure to increase but again allowing little time for any significant increase in LV mass.

Statistical Analysis[25]

Values reported represent the mean ± 1 standard deviation. Analysis of variance was used for multiple group comparisons, followed by a Newmann-Keul multiple range test for comparisons between all pairs of means when an overall significant p value was obtained. Changes in mean arterial pressure and heart rate before and after each flow determination and before and after carbochrome administration were statistically analyzed for each group by a 2-way analysis of variance.

Results

Study 1

Development and reversal of LV hypertrophy: Both blood pressure and LV weight were markedly increased ($p < 0.01$) in untreated hypertensive rats 10 and 24 weeks after clipping (Table I). With prolonged treatment with captopril or after left nephrectomy, both arterial pressure and the LV mass/body weight ratio

TABLE I Arterial Pressure and Left Ventricular Mass in Renal Hypertensive Rats

Groups	Sham 1 (n = 12)	Sham 2 (n = 11)	RHR_1 (n = 17)	RHR_2 (n = 9)	RHR-C (n = 8)	RHR-N (n = 9)
MAP	110 ± 7	111 ± 6	177 ± 26*	164 ± 16*	121 ± 16	132 ± 16
LV/BW	1.9 ± 0.2	2.0 ± 0.1	3.0 ± 0.5*	3.0 ± 0.4*	2.3 ± 0.2	2.4 ± 0.3
BP/LV	58 ± 7	55 ± 5	59 ± 7	56 ± 7	53 ± 5	56 ± 4

* $p < 0.01$ (ANOVA); values for BP/LV were not significantly different among all groups.
Values reported are average ± 1 standard deviation. Groups are defined in study 1. (See text). BP/LV = blood pressure/left ventricular mass; LV/BW = left ventricular mass per gram of body weight; MAP = mean arterial pressure (mm Hg) before first coronary blood flow determination.

were significantly decreased ($p < 0.01$ versus hypertensive untreated rats) to values slightly higher than but not significantly different from those of sham-operated control animals (Table I). LV mass and arterial pressure correlated closely as demonstrated by the highly significant linear correlation found between the LV/body weight ratio and intraarterial pressure ($r = 0.88$, $p < 0.001$) (Fig. 1); the same correlation also was found whether the data from the treated groups (RHR-C + RHR-N) were analyzed separately ($n = 17$, $r = 0.71$, $p < 0.025$) or were included with the other groups. Consequently, the ratio of arterial pressure to LV mass normalized for both weight (blood pressure/LV mass ratio) was equivalent in all groups, treated or untreated (Table I).

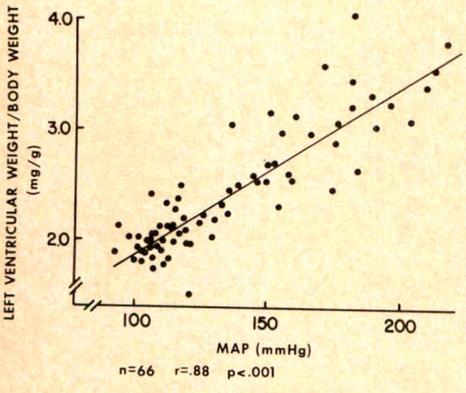

FIGURE 1. A close correlation was found between left ventricular weight (milligram per gram of body weight) and mean arterial pressure (MAP) in all rats (normotensive, hypertensive, and treated hypertensive).

Systemic hemodynamic data (Table II): Resting cardiac output did not differ among the various groups; accordingly, the high blood pressure in the untreated hypertensive rats (RHR_1 and RHR_2) was related to a significant increase in total peripheral resistance ($p < 0.01$ versus control animals). Nephrectomy as well as captopril therapy reduced blood pressure by decreasing resistance.

Carbochrome had no significant effect on arterial pressure, heart rate, or cardiac output; no significant change in any of these indexes was found between pre- and postcarbochrome hemodynamic determinations in any of the groups. The only exception was a modest reduction in blood pressure (−9 mm Hg, $p < 0.01$) in hypertensive rats treated by nephrectomy with no change in either heart rate or cardiac output (Table II).

Coronary hemodynamics: *At rest (Table III):* In the first group of untreated hypertensive rats (RHR_1), resting LVCF/100 g of tissue was higher by approximately 25% compared with its control (Sh_1) ($p < 0.05$). In contrast, resting LVCF was normal in the second group of hypertensive rats studied after 24 weeks of clipping. LV coronary resistance (per 100 g of tissue) was elevated in both hypertensive groups ($p < 0.01$ versus

TABLE II Systemic Hemodynamic Values in Renal Hypertensive Rats Before (b) and After (c) Carbochrome (6 mg/kg)

Group		Sham 1 (n = 12)	Sham 2 (n = 11)	RHR_1 (n = 17)	RHR_2 (n = 9)	RHR-C (n = 8)	RHR-N (n = 9)
Duration (wk)							
Of hypertension		10	24	10	24	9	9
Of treatment		0	0	0	0	15	15†
Body weight (g)		410 ± 36	464 ± 100	350 ± 74	480 ± 79	383 ± 52	440 ± 23
MAP (mm Hg)	b	110 ± 7	111 ± 6	177 ± 26	164 ± 16	121 ± 14	132 ± 16
	c	107 ± 7	111 ± 8	172 ± 30	159 ± 15	128 ± 13	123 ± 15
HR (beats/min)	b	354 ± 35	379 ± 52	379 ± 30	359 ± 37	386 ± 21	376 ± 67
	c	351 ± 35	376 ± 45	375 ± 50	370 ± 33	401 ± 36	392 ± 56
CO (ml/min/kg)	b	357 ± 45	331 ± 46	330 ± 49	320 ± 46	332 ± 21	332 ± 38
	c	359 ± 72	360 ± 47	321 ± 51	349 ± 57	350 ± 44	354 ± 40
TPR (units)	b	0.31 ± 0.04	0.34 ± 0.04	0.55 ± 0.14	0.52 ± 0.10	0.36 ± 0.04	0.41 ± 0.09
	c	0.31 ± 0.06	0.32 ± 0.05	0.56 ± 0.19	0.47 ± 0.09	0.37 ± 0.06	0.35 ± 0.07

* Duration after sham surgery.
† Follow-up after nephrectomy.
Values are means ± standard deviation. All differences between resting determinations (b) and those after carbochrome (c) were not significant except for MAP and TPR in RHR treated by nephrectomy (RHR-N), in which both values decreased slightly after carbochrome ($p < 0.05$). Both MAP and TPR were significantly higher ($p < 0.001$) in the untreated renal hypertensive rats (RHR_1 and RHR_2) than in the other groups (ANOVA).
CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; RHR = renal hypertensive rats; TPR = total peripheral resistance.

TABLE III Coronary Hemodynamics in Renal Hypertensive Rats Before and After Control of Blood Pressure and Regression of Left Ventricular Hypertrophy

Group	Sham 1 (n = 12)	Sham 2 (n = 11)	RHR_1 (n = 17)	RHR_2 (n = 9)	RHR-C (n = 8)	RHR-N (n = 9)
LVCF (ml/min/100 g)						
Rest	381 ± 41	399 ± 101	486 ± 133*	429 ± 72	364 ± 60	419 ± 89
Carbochrome	957 ± 459	1045 ± 485	845 ± 382	923 ± 454	976 ± 490	1142 ± 398
LV coronary resistance (mm Hg/ml/min/100 g)						
Rest	0.29 ± 0.03	0.29 ± 0.06	0.38 ± 0.08†	0.39 ± 0.06†	0.34 ± 0.05	0.33 ± 0.07
Carbochrome	0.14 ± 0.07	0.13 ± 0.06	0.23 ± 0.08‡	0.22 ± 0.12‡	0.17 ± 0.10	0.12 ± 0.04
Total LV coronary resistance (mm Hg/ml/min)						
Rest	15.3 ± 2.6	14.5 ± 3.1	12.9 ± 3.4	13.3 ± 1.8	14.9 ± 2.4	14.0 ± 4.1
Carbochrome	7.2 ± 3.4	6.6 ± 3.4	7.6 ± 2.4	7.2 ± 3.1	7.6 ± 4.6	5.1 ± 1.9

* $p < 0.05$ versus sham 1 (ANOVA).
† $p < 0.01$ versus sham.
‡ $p < 0.05$ versus sham and RHR-N.
Values are means ± standard deviation.
All differences before and after carbochrome within each group were significant ($p < 0.01$); there was no statistically significant difference *among groups* with regard to left ventricular coronary flow (LVCF) after carbochrome or total LV coronary resistance.

sham); however, total LV coronary resistance (per kilogram of body weight) was not significantly different from that of the control group ($p = 0.34$). With reversal of LV hypertrophy, resting LVCF, LV coronary resistance/unit mass, and total LV coronary resistance were within normal values (Table III).

Coronary hemodynamic after carbochrome (Table III): Carbochrome led to significant increases in LVCF and decreases in LV coronary resistance in all groups ($p < 0.01$). The LVCF/unit mass after carbochrome was not significantly different by analysis of variance among all groups of rats ($p = 0.67$). Therefore, LV coronary resistance per unit mass remained elevated in the untreated hypertensive rats ($p < 0.05$). Most importantly, total LV coronary resistance was remarkably similar in all groups ($p = 0.47$) (Fig. 2).

Study 2 (Table IV)

Blood pressure levels were effectively dissociated from LV mass as planned. In group RHRA, the blood pressure/LV mass ratio was diminished because blood pressure had been reduced whereas LV weight was still increased. In group RHRB, exactly the opposite was achieved (Table IV). The ratio of mean arterial pressure to LV mass was averaged 41 ± 7 (standard deviation) in group RHRA versus 63 ± 4 in group RHRB ($p < 0.01$). Both these values were significantly different from each other ($p < 0.01$) and from those obtained in the control groups: Sham A (52 ± 7) and Sham B (53 ± 5) ($p < 0.05$).

Total LV coronary resistance was similar in all groups in this study and not significantly different from values obtained in study 1. However, LVCF/unit mass after carbochrome administration showed a significant reduction in group RHRA compared with group RHRB; more importantly, there was a significant positive correlation between CF after carbochrome administration and the blood pressure/LV mass ratio in these groups ($r = 0.76$, $n = 12$, $p < 0.01$). Thus, CF reserve seemed to diminish when blood pressure was decreased without a corresponding reduction in LV mass.

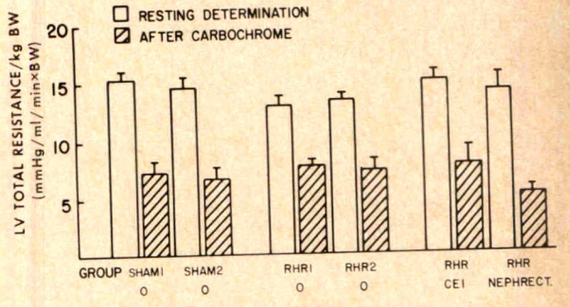

FIGURE 2. The resistance to coronary flow per ventricle (total LV resistance)[4] was not significantly different among any of the groups either at rest or after coronary dilation by carbochrome. BW = body weight; CEI = converting enzyme inhibition; NEPHRECT. = nephrectomy; RHR = renal hypertensive rats.

TABLE IV Dissociation Between Arterial Pressure and Left Ventricular Mass by Therapy in Renovascular Hypertensive Rats: Effect on Coronary Flow

Group	Treatment: Duration (wk)	Treatment: d/c	(MAP (mm Hg)	LV Weight (mg/g)	LVCF (ml/min/100 g): Rest	LVCF (ml/min/100 g): After Carbochrome	Minimal Coronary Resistance: Per 100 g	Minimal Coronary Resistance: Total
A (n = 9)	1	0	115 ± 11	2.9 ± 0.3	411 ± 80	554 ± 113	0.24 ± 0.04	8.3 ± 1.5
B (n = 9)	14	1	153 ± 12	2.4 ± 0.2	446 ± 83	878 ± 232	0.17 ± 0.03	7.2 ± 1.3
p value	. . .		0.01	0.01	NS	0.01	0.01	NS

NS = not significant; d/c = discontinued.

Discussion

The results obtained in this study of renovascular hypertensive rats confirm those reported by Mueller et al[3] in renovascular hypertensive dogs and by Wangler et al[16] in spontaneously hypertensive rats. In all instances, and despite the fact that coronary vasodilation was obtained by adenosine in dogs, by dipyramidole in spontaneously hypertensive rats, and by carbochrome in RHR, LVCF reserve was not significantly altered in hypertensive LV hypertrophy. In all these studies, the minimal total LV coronary resistance remained unchanged despite the large spectrum of variations in LV mass. The present study extends these conclusions further to reversed LV hypertrophy. The absence of significant changes in minimal total LV coronary resistance among our 6 groups of hypertensive rats with various degrees of pressure elevation, alterations in ventricular weight, and therapeutic interventions was a striking observation (Fig. 2, Table III).

Whether the reduction in LV mass was obtained by surgical cure or by medical control of the hypertension, LVCF after maximal carbochrome-induced dilation remained within normal limits. Because it is flow that determines in large measure the oxygen supply to the heart under stress, the CF determined under these conditions was taken as an index of coronary reserve. This term has sometimes been used for the difference between CF at rest and "maximal" CF. However, the use of this definition could unduly subject "flow reserve" to values obtained at rest; if resting CF is increased, this increase would mathematically lead to a reduction in "reserve" despite an unchanged ability of the vessels to dilate.[26]

The maintenance in our experiments of normal CF reserve during the development and after the reversal of LV hypertrophy was tentatively attributed to the appropriate balance observed in this model of hypertension[24,27] between the alterations in arterial pressure and changes in LV mass (Table I, Fig. 2). We hypothesized that under these conditions there would be a near-normal CF reserve; this hypothesis was based on the assumption that under conditions of maximal or near maximal coronary vasodilation, flow becomes a direct dependent of the driving pressure. Because most studies,[3,4,6,16] including the present one, have demonstrated an unchanged minimal total LV coronary vascular resistance (per ventricle) in various models of LV hypertrophy, the ratio of coronary perfusion pressure to LV mass would then be an important determinant of myocardial perfusion. If mass is "appropriate" to the increase in pressure, then CF reserve would be within normal, but if LV mass was greater than expected for the perfusion pressure, maximal CF would be reduced.

This hypothesis was tested by the second protocol in which manipulations of therapy were used to alter the blood pressure/LV mass ratio. Reduction of arterial pressure for too brief a time to alter LV weight was associated with a diminished CF reserve. Reversal of LV hypertrophy was associated with normal CF reserve even when arterial pressure was allowed to increase. The same conclusions could also be deduced from the results reported by Murray and Vatner[28] in dogs with right ventricular hypertrophy secondary to banding of the pulmonary artery. Right ventricular CF reserve was significantly lower than that in control subjects because coronary perfusion pressure was not changed whereas right ventricular mass increased markedly.

Most studies of pressure-overload hypertrophy confirm the original suggestion by Marcus et al[6] that the functional cross-sectional area of the coronary circulation does not grow in parallel with ventricular mass. The reasons for the lack of growth of the coronary functional cross-sectional area with cardiac hypertrophy are not quite clear.[3] There may be little or no change in the coronary vasculature with the development[29,30] or reversal of cardiac hypertrophy. Alternatively, some neovascularization may occur, but the vasodilating capacity of the coronary vessels is impaired by functional factors or structural changes, or both.[3,4,31,32] With reversal of LV hypertrophy and control of blood pressure, these functional and structural factors would presumably be reversed, improving the vasodilatory capacity of each vessel.

Whatever the reasons for the constancy in the functional coronary cross-sectional area, its corollary is that CF reserve becomes dependent on the ratio of coronary perfusion pressure to LV mass, a concept supported by significant correlation found in this study between maximal coronary flow and the ratio of blood pressure to LV mass. If these results prove to be a feature of pressure-overload hypertrophy, this observation could have potentially important clinical implications. Antihypertensive drugs that induce a decrease in mass parallel to their reduction in blood pressure would be preferable, as regards CF reserve, to medications that can control arterial pressure without reducing LV mass.[18–20] Further studies are obviously needed to evaluate these hypotheses. In this context, a direct effect of captopril on the vasodilatory capacity of the coronary vessels is conceivable; however, we could not document any significant effect of captopril on minimal total LV coronary resistance in control rats (unpublished observations). Moreover, neither acute nor chronic converting enzyme inhibition with teprotide or captopril had any discernible effect on the coronary circulation in rats[33] or dogs[34] unless the latter were on a low sodium diet.

Advantages and limitations of this study: CF measurements were performed in conscious rats, and the left atrial injection allowed more precise CF measurements because of better mixing of the microspheres.[21] Carbochrome was used to induce coronary dilation, because it did not alter systemic hemodynamic indexes as adenosine or dipyramidole usually do. Dose-response studies showed that LVCF reached a plateau at doses of 9 and 12 mg/g in normal rats and at the slightly lower doses of 6 or 9 mg/kg in renal hypertensive rats (Table V). Convulsions in both groups of rats became a significant problem at the 9 mg/kg dose level; this problem did not occur with 6 mg/kg and this dose was therefore selected. The assumption that near-maximal coronary vasodilation was achieved at this dose level is based on the basic agreement of our results with regard to the unchanged minimal LV total

TABLE V Coronary Blood Flow After Carbochrome: Normal and Renal Hypertensive Rats (RHR)

Index/Group	Intraatrial Carbochrome (mg/kg) 6	9	12
LV flow (ml/m/100 g)			
Normal rats			
n	8	11	3
Flow	1,047 ± 273	1,334 ± 610	1,524 ± 384
RHR			
n	26	4	. . .
Flow	853 ± 329	907 ± 507	. . .
Coronary resistance			
Normal rats			
n	8	11	3
Units/100 g LV	0.10 ± 0.03	0.09 ± 0.05	0.07 ± 0.02
RHR			
n	26	4	. . .
Units/100 g LV	0.21 ± 0.08	0.18 ± 0.08	. . .

Values given are the average ± 1 standard deviation.
Within each group (normal or RHR) the values obtained at the 3 dose levels for either flow or resistance were not significantly different from each other.

coronary resistance in hypertension, with studies in which maximal coronary vasodilation was achieved.[3,4,28]

The distribution of CF between the endocardium and epicardium was not measured in this study. Therefore, our data do not exclude the possibility of diminished perfusion of the subendocardial layers even when total CF reserve is normal.[10,17,35]

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End-Systolic Dimension-Wall Thickness Relations During Myocardial Ischemia in Conscious Dogs

A New Approach for Defining Regional Function

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Overall and regional left ventricular (LV) function was studied during progressive coronary stenosis in conscious dogs by determining the relations at end-systole between LV pressure, chamber dimensions, and regional LV wall thickness. An index of regional wall stress was also analyzed. Using ultrasonic dimension gauges, measurements were made of LV wall thickness in control and ischemic regions, and the external long- and short-axis LV diameters were determined; an implanted micromanometer measured LV pressure. Internal LV diameters were obtained from the external diameters by subtraction of wall thickness, and the index of regional wall stress employed a thick-walled ellipsoidal model. During regional ischemia, the LV long axis at end-systole did not change, whereas the short-axis diameter progressively increased (from 24 ± 7 mm [standard deviation] to 30 ± 9 mm, p <0.001, indicating a more spherical LV shape during ischemia). The end-systolic pressure did not change, and therefore the end-systolic pressure-diameter relation shifted progressively, suggesting a global decrease in LV contactility. The end-systolic points relating LV wall thickness in the ischemic region to the end-systolic LV pressure revealed the regional nature of the abnormality, showing a progressive displacement to the left, whereas there was no significant displacement of this relation in the control region. The application of this index over a range of loading conditions during partial vena caval occlusion was illustrated. Thus, the regional end-systolic wall thickness-pressure relation provides a new index for defining the regional contractile state of the LV myocardium which is potentially load-independent and offers the possibility for echocardiographic application.

End-systolic measures of left ventricular (LV) function using LV pressure and volume or diameter have recently been shown to provide a load-independent approach to assessing the contractility of the whole heart.[1–4] The end-systolic LV wall thickness-pressure or wall stress relation also can sensitively detect changes in myocardial contractility of the whole ventricle.[5] The regional nature of this measurement suggested that end-systolic indexes based on wall thickness might be useful for assessing overall and regional myocardial function during ischemia, and also might be used to develop an index of regional wall stress for understanding more completely the nature of regional loading conditions during coronary stenosis. Accordingly, the present study analyzes the effects of progressive coronary arterial narrowing on end-systolic LV pressure-dimensions and pressure-wall thickness relations during ischemia in the conscious dog.

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Methods

Animal preparation: Eight mongrel dogs weighing 15 to 44 kg were anesthetized with sodium pentobarbital (25 to 30 mg/kg, intravenously). A thoracotomy was performed in the fifth intercostal space, and, using sterile technique, the animals were prepared for chronic studies. A high fidelity micromanometer (Konigsberg® P-7) and a small catheter were placed into the LV chamber through a stab wound near the apex.[6] The left circumflex coronary artery was dissected free near its origin and a hydraulic cuff was placed around the

vessel. For the continuous measurement of the external LV long axis, a pair of ultrasonic crystals was implanted at the base and apex, the base crystal being placed in the groove between the aortic root and the left atrium and the other crystal at the apical dimple.[7] A second pair of crystals was sutured to the epicardium of the anterior and posterior walls for the measurement of the external LV short axis. To obtain regional wall thickness, a third pair of miniature crystals was placed in the LV posterior wall in the center of the region perfused by the left circumflex coronary artery (designated as ischemic wall thickness), using a technique described previously.[8] One of the crystals was inserted tangentially through the myocardium into the subendocardium, and the other was sutured to the epicardial surface opposite the inner crystal at a site where the ultrasonic transit time was shortest between the 2 crystals. This technique allowed the placement of the crystals across the LV wall without damage to the intervening tissue and provided highly accurate wall thickness measurements which sensitively reflect various degrees of myocardial ischemia.[9,10] Another pair of crystals was placed in the anterior wall in the same manner and designated as control wall thickness. Both wall thickness pairs were positioned as close as possible to the crystals of the short axis. The position of the crystals used for diameter measurements and the wall thickness pairs was examined at necropsy and confirmed to be in proper alignment directly across the wall, with the inner crystal within 2 mm of the endocardial surface. The chest was then closed; all wires and tubes were passed subcutaneously to the back of the dog and brought through the skin between the scapulae.

Experimental protocol: Studies were performed 2 to 3 weeks after operation, when the dog was vigorous and healthy, and with the dog resting quietly on its right side on the floor. After control measurements were recorded in the resting state, a level of partial coronary stenosis was created with the hydraulic occluder placed on the left circumflex coronary artery using a screw-driven syringe. After stable hemodynamic and dimension conditions were attained for at least 2 minutes, measurements were obtained. The stenosis was released and the dog was then allowed to recover for at least 30 minutes. Several different levels of partial coronary stenosis were obtained in the same manner. Because it was difficult to create the same level of partial coronary stenosis in each dog, the degrees of coronary stenosis were categorized on the basis of the systolic wall thickening in the ischemic region. The levels of partial coronary stenosis were divided into 4 groups: (1) wall thickening reduced <60%, (2) wall thickening reduced 60 to 80%, (3) wall thickening reduced >80%, and (4) complete coronary occlusion (performed for 2 minutes).

Recordings were monitored continuously on a multichannel recorder and stored on magnetic tape for subsequent data analysis by computer. The dimension signals were calibrated by an electrical pulse of precisely known duration derived from a stable crystal controlled oscillator.[11] The micromanometer was calibrated by matching it to the pressure obtained through a fluid-filled catheter connected to the pressure gauge (Statham P-23Db) at the beginning and end of each study with frequent calibration checks throughout the study by known electrical voltages.

Data analysis: Analog signals played back from the magnetic tapes were digitized every 5 ms through an analog-to-digital converter and fed to a computer system with a microprocessor (DEC, LSI-11) and digital plotter (HP, 7221B). At least 10 beats were averaged, the reference signal being the first derivative of LV pressure (dP/dt), and beats with a duration >100 ms from the average were excluded from the averaging process.

The measured wall thicknesses of the ischemic region (IWTh) and of the control region (CWTh) were used to obtain the LV internal (int) long-axis diameter (LAD) and short-axis diameter (SAD) by subtraction from external (ext) diameters[7]: LADint = LADext − 1.1 × CWTh, and SADint = SADext − CWTh − IWTh. An index of regional wall stress (WSt) in both the control and ischemic regions was estimated from a thick-walled ellipsoidal model using the wall thickness in the control or the ischemic region: $WSt = p \times SADint \times 1 - 0.5 \times (SADint/LADint)^2/(2 \times WTh)$,[12] where P = LV pressure. As an index of global wall stress, the value was calculated using the same equation by employing the mean value of both wall thicknesses. The first derivative of wall stress (dWSt/dt) during ejection was computed at the time of maximal velocity of shortening of the internal short-axis diameter.

It is recognized that calculation of the true regional wall stress will require knowledge of local radii of curvature and that our approach represents only an estimate. Moreover, it is apparent that use of a single point in the ischemic region and another from the control wall to determine the LV short axis is subject to potential error. Thus, this approach assumes that an entire one half of the left ventricle is represented by the ischemic wall, whereas it is not likely that this was the case, particularly with less severe stenoses. The most powerful determinant of regional wall stress under these conditions, however, should be the regional wall thickness. Accordingly, the maximal error in end-systolic wall stress that could have been introduced by overestimation of the minor axis was determined by calculating end-systolic wall stress at the 4 levels of ischemia using the control (prestenosis) end-systolic ventricular diameter at each point together with the measured wall thickness during ischemia; these errors were 6.1 ± 3.1% (standard deviation [SD]) in mild stenosis, 10 ± 3.2% in moderate, 12 ± 4.5% in severe, and 15 ± 5.0% with complete coronary occlusion. Thus, despite this potential for modest overestimation of wall stress, the consistently large increases observed in the end-systolic wall stress index lend validity to the directional changes of wall stress in the ischemic region that we report.

To cancel out size dependencies of the left ventricle among the dogs, normalization of LV diameters was performed with respect to the LV muscle mass obtained at necropsy, the measured diameter being divided by the LV mass and multiplied by 100.[13] The wall thickness was normalized to a 10 mm initial thickness by dividing the measured thickness by the control resting end-diastolic thickness and multiplying by 10.[14] Velocities of a given parameter were normalized to the instantaneous value of the parameter and the peak value was used for analysis. End-diastole was identified at the point just before the onset of the positive dP/dt of the left ventricle, and end-systole at the point of maximal systolic excursion of the control wall thickness, occurring at or within 20 ms before peak negative dP/dt.[10,14]

Dynamic loops (X-Y plots) of various parameters during a cardiac cycle were generated by a computer-aided digital plotter from averaged beats.

Statistical analysis was done with an analysis of variance for repeated measures followed by the Bonferroni method of multiple comparisons, a p value <0.01 being considered significant.[15,16] All data are expressed as mean ± standard deviation unless otherwise stated.

Results

A typical example of original recordings from which the data were measured and computed is shown in Figure 1, illustrating the effect of various levels of re-

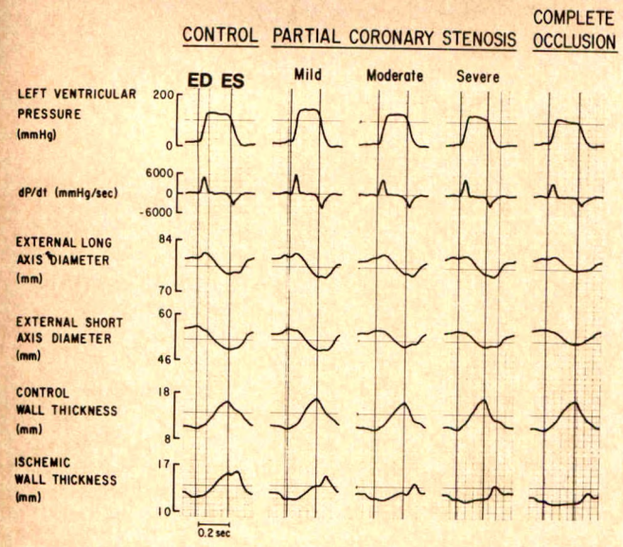

FIGURE 1. Representative original recording. The LV pressure, dP/dt, the external long- and short-axis diameters of the left ventricle, and the wall thickness in control and ischemic regions were simultaneously recorded in a conscious dog, and stored on magnetic tape for further processing by computer. After the control recording (**first panel**), stable conditions at various levels of myocardial ischemia were achieved by adjusting the hydraulic occluder on the left circumflex coronary artery (**3 middle panels**). Complete coronary occlusion was also performed (**last panel**). Note the progressive deterioration in systolic thickening of the ischemic wall and reduction of systolic shortening of the short-axis diameter during ischemia, with little change in control wall thickness and long-axis diameter. ED = end-diastole; ES = end-systole.

gional myocardial ischemia on the LV pressure, external long- and short-axis diameters, and wall thickness in the control and ischemic regions. The averaged LV hemodynamic and dimension data are summarized in Tables I and II and data on regional LV wall thickness and wall stress are shown in Table III.

Hemodynamic changes: During the 4 levels of myocardial ischemia, the peak and end-systolic LV pressure and its derivative were not significantly changed, and only during complete coronary occlusion was the end-diastolic pressure significantly elevated to 18 ± 6.2 mm Hg ($p < 0.001$) from control (9.9 ± 2.0, Table I). Heart rate increased with increasing severity of ischemia, being significantly elevated during severe stenosis and complete occlusion.

LV dimensions: The external and internal dimensions of the LV long axis were little affected by regional myocardial ischemia and only complete coronary occlusion induced significant decreases in systolic shortening extent and velocity of the long axis (Table I). The short axis showed progressive and significant increases in external and internal end-systolic diameters during ischemia, with significant deterioration of systolic shortening and peak systolic shortening velocity during the first level of coronary stenosis (Table I), while the end-diastolic diameters remained unchanged as the heart rate progressively increased. During myocardial ischemia, the ratio of the LV short-axis diameter to the long-axis diameter at end-systole was significantly increased while the ratio at end-diastole was not changed,

TABLE I Effects of Partial and Complete Coronary Occlusion on Left Ventricular Hemodynamics and Dimensions

		Partial Coronary Stenosis			
	Control	Mild	Moderate	Severe	Complete CO
Heart rate (beats/min)	88 ± 14	96 ± 17*	104 ± 13*	119 ± 19†	124 ± 23†
LVP (mm Hg)					
ED	9.9 ± 2.0	12 ± 3.7*	12 ± 5.5*	14 ± 5.5*	18 ± 6.2†
Peak	128 ± 11	127 ± 13*	127 ± 14*	126 ± 15*	130 ± 22*
ES	114 ± 14	110 ± 12*	113 ± 14*	110 ± 15*	116 ± 21*
dP/dt (mm Hg/s)	3,414 ± 490	3,060 ± 457*	3,055 ± 350*	3,170 ± 431*	3,058 ± 570*
LADext					
ED	70 ± 18	70 ± 17.9*	71 ± 18*	71 ± 18*	70 ± 18*
ES	67 ± 17	68 ± 17*	68 ± 17.0*	68 ± 17*	68 ± 17*
% Shortening	4.2 ± 1.7	3.9 ± 1.4*	3.7 ± 1.2*	3.3 ± 1.2*	2.7 ± 1.4†
Shortening velocity	0.60 ± 0.12	0.56 ± 0.12*	0.53 ± 0.09*	0.52 ± 0.11*	0.46 ± 0.13
LADint					
ED	61 ± 16	61 ± 15.9*	61 ± 16*	61 ± 16*	61 ± 16*
ES	55 ± 15	55 ± 15*	55 ± 15*	55 ± 14*	56 ± 15†
% Shortening	10 ± 3.6	10.1 ± 3.6*	9.9 ± 3.4*	9.5 ± 3.1*	8.7 ± 2.9†
Shortening velocity	1.2 ± 0.31	1.1 ± 0.37*	1.1 ± 0.35*	1.1 ± 0.34*	0.99 ± 0.25†
SADext					
ED	53 ± 12	53 ± 12*	54 ± 12	53 ± 12*	54 ± 12*
ES	48 ± 11	50 ± 11‡	50 ± 11†	50 ± 11†	51 ± 12†
% Shortening	8.9 ± 2.3	7.4 ± 2.4‡	6.8 ± 2.0†	5.8 ± 1.6†	5.0 ± 18†
Shortening velocity	0.81 ± 0.15	0.76 ± 0.17*	0.71 ± 0.16‡	0.62 ± 0.14†	0.56 ± 0.12†
SADint					
ED	35 ± 9.2	35 ± 9.1*	35 ± 9.2*	35 ± 9.3*	35 ± 9.3*
ES	24 ± 7.4	27 ± 8.4†	28 ± 8.4†	29 ± 8.8†	30 ± 9.1†
% Shortening	31 ± 8.3	25 ± 9.3†	21 ± 7.4†	18 ± 6.3†	16 ± 6.5†
Shortening velocity	3.2 ± 1.1	2.7 ± 1.1‡	2.3 ± 0.85†	2.1 ± 0.86†	1.8 ± 0.59†

Data are mean ± standard deviation.
* p = not significant.
† $p < 0.001$.
‡ $p < 0.01$.
CO = coronary occlusion; dP/dt = peak positive first derivative of left ventricular pressure (LVP); ED = end-diastole; ES = end-systole; ext = external diameters; int = internal diameter; LAD = long axis diameter of left ventricle (mm); peak = peak value during systole; SAD = short-axis diameter of left ventricle (mm); % shortening = percent shortening during systole; shortening velocity = peak normalized velocity of diameter shortening (diameter/s).

TABLE II Ratio of Short- and Long-Axis Diameters of the Left Ventricle

	Control	Partial Coronary Stenosis			Complete CO
		Mild	Moderate	Severe	
External SAD/LAD					
ED	0.77 ± 0.05	0.76 + 0.06*	0.76 ± 0.05*	0.77 ± 0.05*	0.77 ± 0.05*
ES	0.73 ± 0.05	0.73 ± 0.05*	0.74 ± 0.05†	0.75 ± 0.05‡	0.75 ± 0.05‡
Internal SAD/LAD					
ED	0.58 ± 0.05	0.58 ± 0.06*	0.58 ± 0.05*	0.58 ± 0.05*	0.58 ± 0.05*
ES	0.45 ± 0.07	0.48 ± 0.08‡	0.51 ± 0.07‡	0.53 ± 0.06‡	0.54 ± 0.07‡

Data are mean ± standard deviation.
* p = not significant.
† p <0.01.
‡ p <0.001.

indicating that the left ventricle became more spherical during systole in the presence of ischemia compared with control (Table II).

Regional LV wall thickness: End-systolic wall thickness in the ischemic region was decreased to 12 ± 0.44 mm (p <0.001) during mild coronary stenosis from 13 ± 0.62 mm (control) and gradually decreased further with more severe ischemia; end-diastolic wall thickness was not significantly changed (Fig. 2, Table III). Wall thickening extent during systole was reduced by 52% in mild stenosis, 77% in moderate stenosis, and 96% in severe stenosis, and it was replaced by systolic thinning during complete coronary occlusion (Fig. 2). The peak wall thickening velocity during systole was also markedly decreased during myocardial ischemia (Fig. 2). Wall thickness in the control area, however, showed no significant changes in thickness at end-diastole and end-systole, or in systolic thickening extent and velocity (Fig. 2, Table III).

A representative example of the relations between ischemic wall thickness and LV pressure throughout the cardiac cycle is shown in the left panel of Figure 3 (end-systolic points are indicated by asterisks). During control, the loop rotated clockwise during ventricular systole. During partial coronary stenosis, the extent of systolic wall thickening decreased, producing a leftward shift of the loop, and the wall thinned and then thickened again late in systole as ventricular pressure decreased. During complete coronary occlusion, the loop area became nearly zero, suggesting passive deformation.

End-systolic relation: End-systolic LV pressure did not change significantly during progressive coronary stenosis while end-systolic internal short axis of the ventricle progressively increased (Table III), a finding which suggests that depression of global contractility is produced by ischemia since contractility changes are known to shift this relation. Assessment of the relations between regional wall thickness and LV pressure at end-systole in the ischemic zone showed a progressive shift to the left of this relation with increasing coronary stenosis (Fig. 4, top left), indicating progressive regional wall thinning at end-systole at a constant end-systolic pressure, whereas this relation remained unchanged in the control region (Fig. 4, bottom left, Table III).

Linear end-systolic relations between the LV pressure and wall thickness found previously under normal conditions[5] also are shown in Figure 4 (thick dotted line).

Regional wall stress index: The index of regional wall stress and the rate of wall stress change (dWSt/dt) during systole in the control region were not affected by myocardial ischemia (Fig. 5, Table III). The index of regional wall stress in the ischemic region showed a significant increase during ischemia, with the peak wall stress index significantly greater than control during severe coronary stenosis and during complete occlusion. The end-systolic wall stress index increased earlier and more markedly, being significantly increased during mild stenosis (160 ± 42 g/cm^2, compared with a control value of 134 ± 34 [p <0.01]); it increased substantially

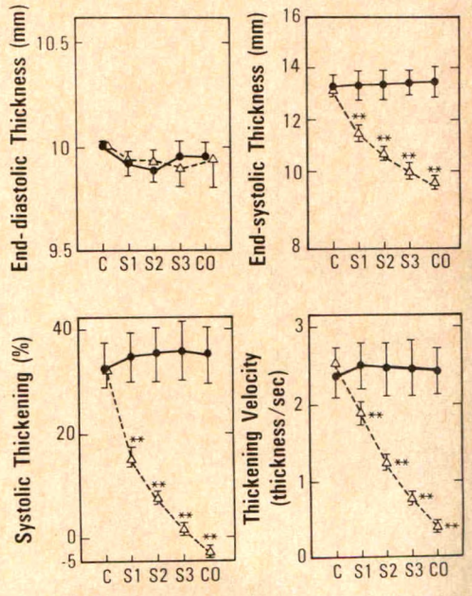

FIGURE 2. Mean values of regional wall thickness in the control (**closed circles**) (mean ± standard error of the mean) and ischemic regions (**open triangles**). End-diastolic wall thickness (**top left**) showed no significant changes during ischemia. End-systolic wall thickness (**top right**) in the ischemic region decreased significantly with progression of the severity of ischemia accompanied by the progressive deterioration in the systolic wall thickening (**bottom left**), as well as in systolic thickening velocity (**bottom right**). No changes were observed in these parameters in the control region. C = control; S1, S2, S3 = mild, moderate, and severe stenosis, respectively; CO = complete occlusion. * p <0.01, ** p <0.001, in comparison with control.

TABLE III Effects of Partial and Complete Coronary Occlusion on Regional Left Ventricular Dimensions

		Partial Coronary Stenosis			
	Control	Mild	Moderate	Severe	Complete CO
End-systolic LV pressure	114 ± 14	110 ± 12*	113 ± 14*	110 ± 15*	116 ± 21*
End-systolic SADint	24 ± 7.4	27 ± 8.4†	28 ± 8.4†	29 ± 8.6†	30 ± 9.1†
Wall thickness in control region					
ED	10	9.9 ± 0.2*	9.9 ± 0.16*	10 ± 0.20*	10 ± 0.2*
ES	13 ± 1.4	13 ± 1.5*	13 ± 1.5*	13 ± 1.4*	14 ± 1.6*
% Thickening	33 ± 14	35 ± 14*	36 ± 15*	36 ± 16*	35 ± 16*
Thickening velocity	2.4 ± 0.88	2.5 ± 0.94*	2.5 ± 0.99*	2.5 ± 1.1*	2.4 ± 0.93*
Wall thickness in ischemic region					
ED	10	9.9 ± 0.1*	9.9 ± 0.2*	9.9 ± 0.3*	9.9 ± 0.4*
ES	13 ± 0.62	12 ± 0.4†	11 ± 0.1†	10 ± 0.3†	10 ± 0.4†
% Thickening	32 ± 6.2	16 ± 5.1†	7.5 ± 2.5†	1.2 ± 2.0†	−3.7 ± 1.2†
Thickening velocity	2.6 ± 0.60	1.9 ± 0.45†	1.3 ± 0.26†	0.76 ± 0.19†	0.40 ± 0.15†
Wall stress index in control region					
ED	23 ± 8.8	29 ± 10*	29 ± 12*	32 ± 12*	42 ± 12†
Peak	267 ± 80	267 ± 82*	269 ± 80*	268 ± 78*	278 ± 85*
ES	154 ± 54	158 ± 57*	168 ± 55*	166 ± 58*	182 ± 66†
dWSt/dt	−1,071 ± 381	−936 ± 416*	−869 ± 357*	−920 ± 335*	−883 ± 281*
Wall stress index in ischemic region					
ED	20 ± 5	26 ± 8*	26 ± 12*	28 ± 9.1*	38 ± 13†
Peak	240 ± 48	252 ± 46*	262 ± 51*	268 ± 53‡	283 ± 68†
ES	134 ± 34	160 ± 43‡	185 ± 51†	194 ± 49†	220 ± 59†
dWSt/dt	−1,039 ± 230	−860 ± 301*	−669 ± 196†	−638 ± 249†	−520 ± 302†
Mean wall stress of left ventricle	254 ± 53	259 ± 53*	266 ± 54*	268 ± 52*	280 ± 63§

Data are mean ± standard deviation.
* p = not significant.
† p <0.001.
‡ p <0.01.
§ p <0.005.
dWSt/dt = first derivative of wall stress at time of peak ventricular ejection (g/cm²/s); mean wall stress = estimated global wall stress using mean wall thickness (g/cm²). % thickening = percent wall thickening during systole; thickening velocity = peak normalized velocity of wall thickening during systole (thickness/s); wall stress index = an index of regional wall stress in each region (g/cm²). Wall thickness in millimeters. Other abbreviations as in Table I.

further with the progression of ischemia (Fig. 5). The dWst/dt in the ischemic area during ejection also decreased significantly during ischemia (Fig. 5).

The mean wall stress of the entire left ventricle showed little change during myocardial ischemia, and it increased significantly only during complete occlusion (Table III).

The relation between ischemic wall thickness and the index of wall stress in the ischemic region had a clockwise rotation, with wall stress decreasing during systole (Fig. 3, right). With progression of ischemia, the loops shifted upward and to the left, accompanied by increases in the peak and end-systolic wall stress indexes. These loops of regional wall thickness versus the index of regional wall stress (Fig. 3, right) provide some insight into the characteristics of regional loading conditions during progressive coronary stenosis. While systolic LV pressure during ejection tended to decrease in this example as ischemia developed (Fig. 3, left), there was an increase in the peak wall stress index and a more marked increase in the end-systolic wall stress index. Thus, the local contractile defect, by diminishing systolic wall thickening, leads to regional systolic loading during ejection, which could further impair the regional reduction in shortening produced by ischemia itself.

The relations at end-systole between the index of regional LV wall stress and the corresponding wall thickness in control and ischemic regions are summarized in the right panels of Figure 4 and in Table III. A significant leftward and upward shift of the relation occurred in the ischemic region, whereas no change was observed in the control region.

Discussion

The description and quantification of local changes in myocardial function appears essential to an understanding of the effect of various experimental and clinical therapeutic approaches designed to improve myocardial performance and reduce tissue damage during myocardial ischemia. The regional nature of myocardial dysfunction associated with ischemia due to coronary obstruction has been recognized since the original description of aneurysmal bulging in the area distal to an experimental coronary occlusion by Tennant and Wiggers.[17] Miniature ultrasonic crystals implanted in the LV subendocardium have been used to characterize regional contractile function and segment lengths in various regions of the left ventricle during acute coronary occlusion.[11,18,19] The ultrasonic dimension gauges have also proven to be highly suitable for the analysis of regional myocardial function using continuous measurements of regional wall thickness during myocardial ischemia[8,9,20]; echocardiography has also been used for this purpose.[21]

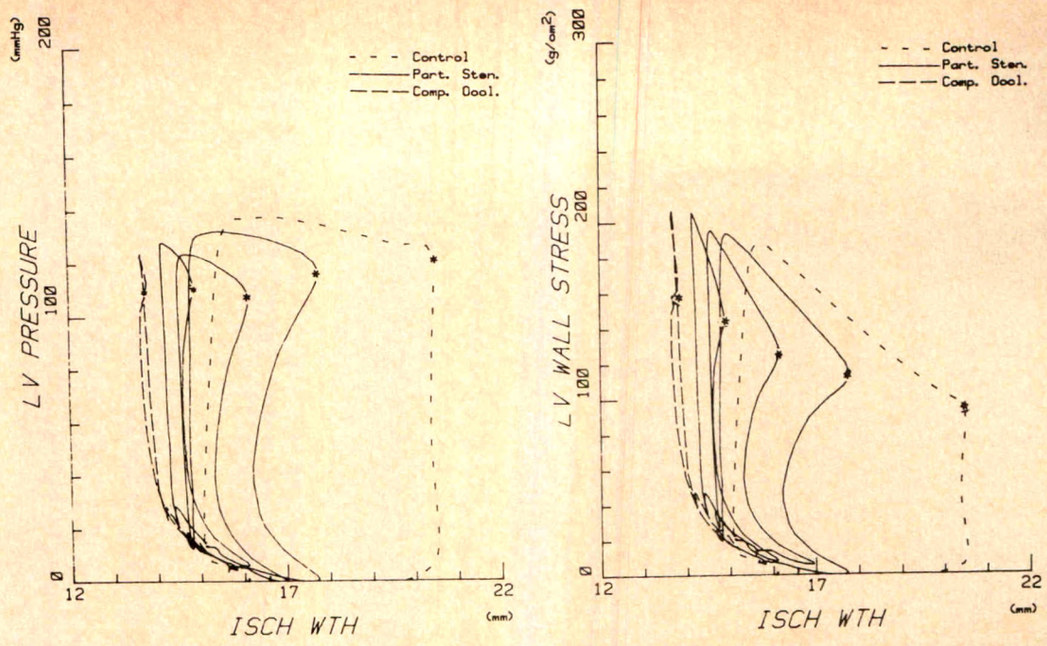

FIGURE 3. A typical computer plot of the relations between ischemic wall thickness (ISCH WTH) and left ventricular (LV) pressure (**left**) or wall stress index (**right**). **Short dashed lines,** control data; **solid lines,** partial stenosis (Part. Sten.); **long dashed lines,** complete occlusion (Comp. Occl.); **asterisks,** end-systole. During control, the normal loops rotate clockwise. During partial stenosis, reduced systolic wall thickening and marked thickening during isovolumic relaxation are apparent. During complete occlusion, systolic thickening was replaced by wall thinning and the area within the loop was near zero. While peak and end-systolic left ventricular pressure decreased a little during ischemia, end-systolic wall stress increased much more than the increase of peak stress. Thus, the loops of LV pressure-wall thickness shifted to the left of control during ischemia, while the loops of wall stress-wall thickness showed the end-systolic points to be displaced upward and to the left.

Recent studies comparing regional coronary blood flow distribution measured by the microspheres technique with regional systolic wall thickening show a close correlation between reductions in subendocardial blood flow and the degree of impairment of contractile function.[10] Although regional blood flow was not measured in the present study, the characteristics of regional wall thickness dynamics measured with the ultrasonic dimension gauges appear reliable for detecting changes in regional myocardial perfusion[10] and also were shown

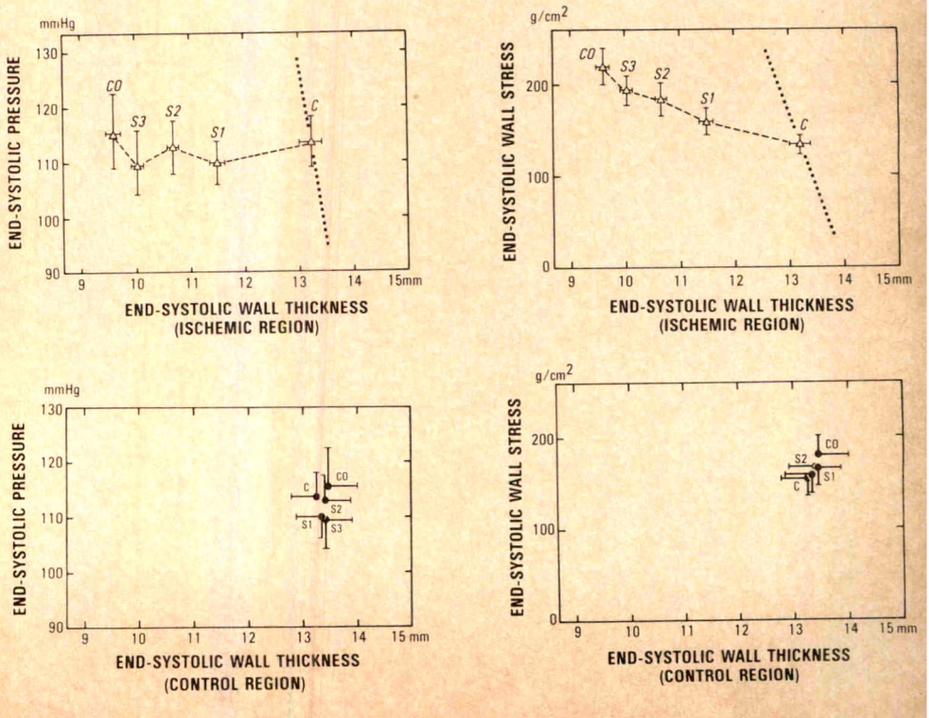

FIGURE 4. Summary of end-systolic relations between the LV wall stress index (**right panels**) or LV pressure (**left panels**) versus wall thickness in the control (**bottom panels**) or ischemic regions (**top panels**). Notations as in Figure 2. **Thick dashed lines** at control in top panels show the average relations between the end-systolic LV pressure or wall stress and wall thickness obtained in our previous experiments (see text). With the progression of ischemia, the end-systolic points of wall stress index and wall thickness in the ischemic region were markedly shifted leftward and upward of control, and the points of LV pressure and wall thickness in the ischemic region were shifted to the left of control, while no significant displacement was observed in the control region, suggesting that the myocardial contractility was decreased in the ischemic region but not in the control region.

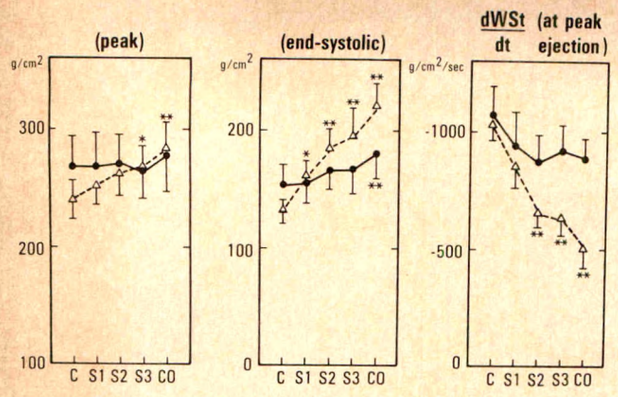

FIGURE 5. Summary of changes in the index of regional wall stress. Symbols and notations as in Figure 2. The end-systolic wall stress (**center**) in the ischemic region increased significantly during all levels of myocardial ischemia, while the peak wall stress (**left**) increased only in severe ischemia. The wall stress in the control region showed little change. The first derivative of wall stress in the ischemic region during peak systolic ejection (**right**) decreased significantly with the progression of ischemia.

to be more sensitive than surface electrocardiographic changes.[22] In the present study, we used regional wall thickening dynamics during systole together with data on overall LV dimensions to analyze global and regional myocardial function during ischemia within a framework of end-systolic pressure, dimensions, and an index of regional wall stress.

End-systolic measures of LV function have recently been investigated for assessing the contractility of the heart in both animal and human subjects.[1–4] In these reports, the end-systolic LV pressure or wall stress was found to be linearly related to the end-systolic LV volume or diameter, and the relations were shifted by changes in myocardial contractility. This type of approach was extended to the relations between the end-systolic LV pressure versus wall thickness, and end-systolic LV wall stress versus wall thickness in the conscious animal,[5] and it was concluded that the relative position of such relations was indicative of the level of inotropic state. Thus, the end-systolic pressure or wall stress versus wall thickness relation was shifted rightward by enhanced myocardial contractility and leftward by reduced contractility.[5] These findings offered the possibility of applying these local wall thickness relations for assessing global LV contractility, when localized regional contraction abnormalities were absent, without the need to determine chamber dimensions or volume. The regional nature of such measurements should also be useful in understanding the effects of myocardial ischemia on contractile function. In the present study, a shift of the LV end-systolic pressure–dimension relation suggested overall depression of contractility. As shown in Figure 4, the end-systolic wall thickness-pressure points in the ischemic region during various levels of coronary stenosis shifted to the left of the control point, indicating progressively decreasing myocardial contractility in that region, whereas little displacement of the end-systolic points in the control region indicated that regional contractility was not affected at that site.

To further illustrate the validity of this approach, in 3 dogs end-systolic relations were determined over a range of loading conditions, in addition to the single

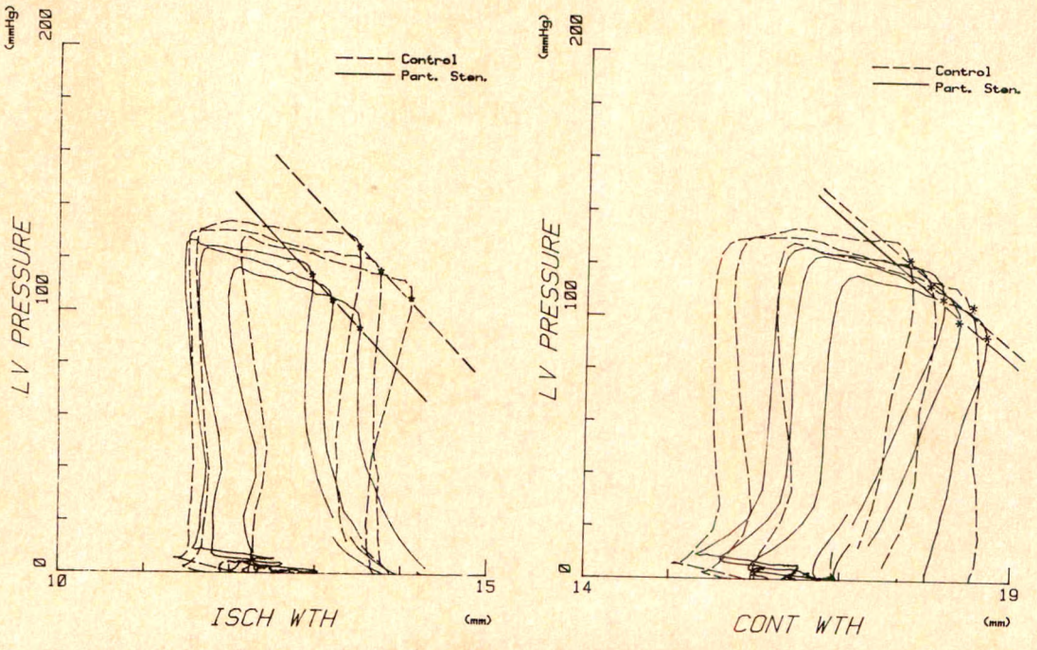

FIGURE 6. An example of computer plotted loops of wall thickness and left ventricular pressure in the control region (**right**) and in the ischemic region (**left**). During the control state (**dashed loops**), reduction in the afterload by vena caval obstruction yielded linear end-systolic relations (**dashed lines**). During partial coronary stenosis (**solid loops**), the linear relation in the ischemic region was shifted to the left of control in a parallel manner (**solid line**), while no change was observed in the control region. Abbreviations as in Figure 3.

point determinations, by producing partial occlusion of the inferior vena cava by means of a hydraulic cuff. This produced some reduction in preload and afterload during both the control state and partial coronary stenosis. A typical example of this procedure is shown in Figure 6. Several beats were sampled during the transient decrease of preload and afterload in the early phase of partial vena caval obstruction, before the occurrence of reflex tachycardia; such a short and transient change should induce little change in the level of ischemia.[18] Without coronary stenosis, the end-systolic points of the loops of wall thickness versus LV pressure in the region to be rendered ischemic showed a linear relation (Fig. 6, left, dashed line). During partial coronary stenosis, the linear end-systolic relation during caval occlusion was shifted downward and to the left of control in a parallel manner (Fig. 6, left, solid line). The end-systolic points in the control region showed a similar linear relation but were not shifted by ischemia (Fig. 6, right). Thus, the end-systolic regional wall thickness–pressure relation (or calculation of their ratio) can sensitively describe regional differences in myocardial contractility, regardless of loading conditions, supporting the usefulness of this relation as a load-independent index for assessing regional myocardial contractility.

Myocardial wall stress in an important determinant of the intrinsic function of myocardium,[23] and myocardial wall forces are a major determinant of energy utilization by the heart.[24] Various techniques have been used to calculate LV wall stress with geometric reference figures. These approaches have varied from the use of a thin-walled spheroid[25,26] or an ellipsoid of revolution[27,28] to treatment of the ventricle as a thick-walled passive elastic body.[29,30] More recently, such analyses have been extended to include consideration of fiber angle distribution within the LV wall.[31,32] The evaluation of myocardial wall stress in the intact ventricle is difficult, since the left ventricle is an irregularly shaped thick-walled structure composed of a continuum of fibers. In generating myocardial wall tension, these fibers undergo rearrangements and shear during the cardiac cycle.[9,33] Nevertheless, investigators have estimated myocardial wall stress by a variety of techniques. Most of them assume that the ventricle is a thick-walled ellipsoid of revolution and that it is composed of an isotropic homogeneous layer of muscle.[27,34] Although these applications of the basic Laplace relation to thick-walled structures can involve appreciable error,[27] the close agreement between measured wall stress and wall stress calculated from geometrical assumptions has been confirmed.[12] In the present study, an index of regional wall stress in both the control and ischemic regions was estimated with the thick-walled ellipsoidal equation using the wall thickness in either the control or the ischemic region. It is appreciated that this approach provides only an approximation, since local radius of curvature is unknown, but the estimated values show directionally appropriate changes during ischemia (see Methods section), and provide some insight into alterations in regional loading. With progressively more severe myocardial ischemia, although the global wall stress index was little changed, the index of wall stress in the ischemic region during systole was significantly increased; the end-systolic wall stress increased much more than the peak value, indicating that wall stress in the ischemic region was sustained at an elevated level throughout systole. This finding characterizes qualitatively for the first time a phenomenon in which regional loading is altered by the ischemic intervention, with systolic wall thinning leading to higher local afterload which must lead to further mechanical impairment of regional function by way of the force-velocity-length relation. Thus, the maintenance of normal systolic pressure by shortening in unaffected regions of the ventricle produced progressive regional systolic wall thinning in the involved zone, and thereby elevated the regional wall stress index. It is postulated that this load-dependent effect contributed to the striking decrease in the velocity and extent of wall thickening in the ischemic zone (Fig. 2).

In summary, end-systolic relations between wall thickness and LV pressure were progressively displaced in ischemic regions but not in control regions during increasing degrees of regional myocardial ischemia. This approach offers the possibility of a relatively load-independent measure of local myocardial contractility in various regions of the ventricle. It should be recognized, however, that if true regional wall stress could be calculated it would more accurately define the afterload. Clinical application of end-systolic measures using wall thickness should be feasible with techniques recently developed in echocardiography and 2-dimensional echocardiographic approaches coupled with systolic pressure measurements[4] also should make it feasible to evaluate regional myocardial function and contractility simultaneously in both impaired and normal myocardium during a variety of interventions.

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MYTH: Fluid-filled catheters are an inexpensive and dependable means of measuring patient blood pressure.

FACT: When accurate patient diagnosis is at stake, "inexpensive" can be costly. Catheter-tip pressure transducers give substantially better accuracy and patient information at a *lower cost per use.*

There is a myth in the medical community that fluid-filled catheters are less expensive to use than catheter-tip pressure transducers.

But that myth is deceiving. The purchase price of a fluid-filled, disposable catheter can be one-seventh that of a reusable, catheter-tip pressure transducer.[1] But the catheter-tip pressure transducer can often give you twenty-five or more uses.[2] So, when the cost of use and not just the purchase price alone is examined, the "more expensive" catheter-tip pressure transducer is actually about half the cost per use of the fluid-filled catheter.

[1]Based on a Millar catheter-tip pressure transducer (Model PC-350).

[2]With the Millar MIKRO-TIP® pressure transducer with the new MT-10™ sensor, multiple usage is greatly increased. The new MT-10™ sensor sets the standard for ruggedness and durability in catheter-tip pressure transducers.

Accuracy and dependability bring the true cost of a catheter-tip pressure transducer even lower. With Millar MIKRO-TIP® catheter-tip transducers, you get an accurate reading the first time. Valuable man-hours are saved, and even more savings are available due to the increased number of measurements that can be performed.

With Millar MIKRO-TIP® catheter-tip transducers, you can forget:

- Time-consuming "debubbling"[3] of the measuring system before catheterization can begin
- Contending with a complicated, often messy, and usually inconvenient fluid-filled system
- Damping of the pressure signal due to changes of the fluid in the tubes, or air infiltration of the system
- Disturbance of the signal and, consequently, less accurate blood pressure measurements caused by the position of the transducer or movement of the patient

What you can depend on is easy-to-use, consistent, dependable, accurate readings of blood pressure — at the source — and at a cost per use much lower than you've been led to believe.

[3]i.e. debubbling tubing, stopcock connection, etc.

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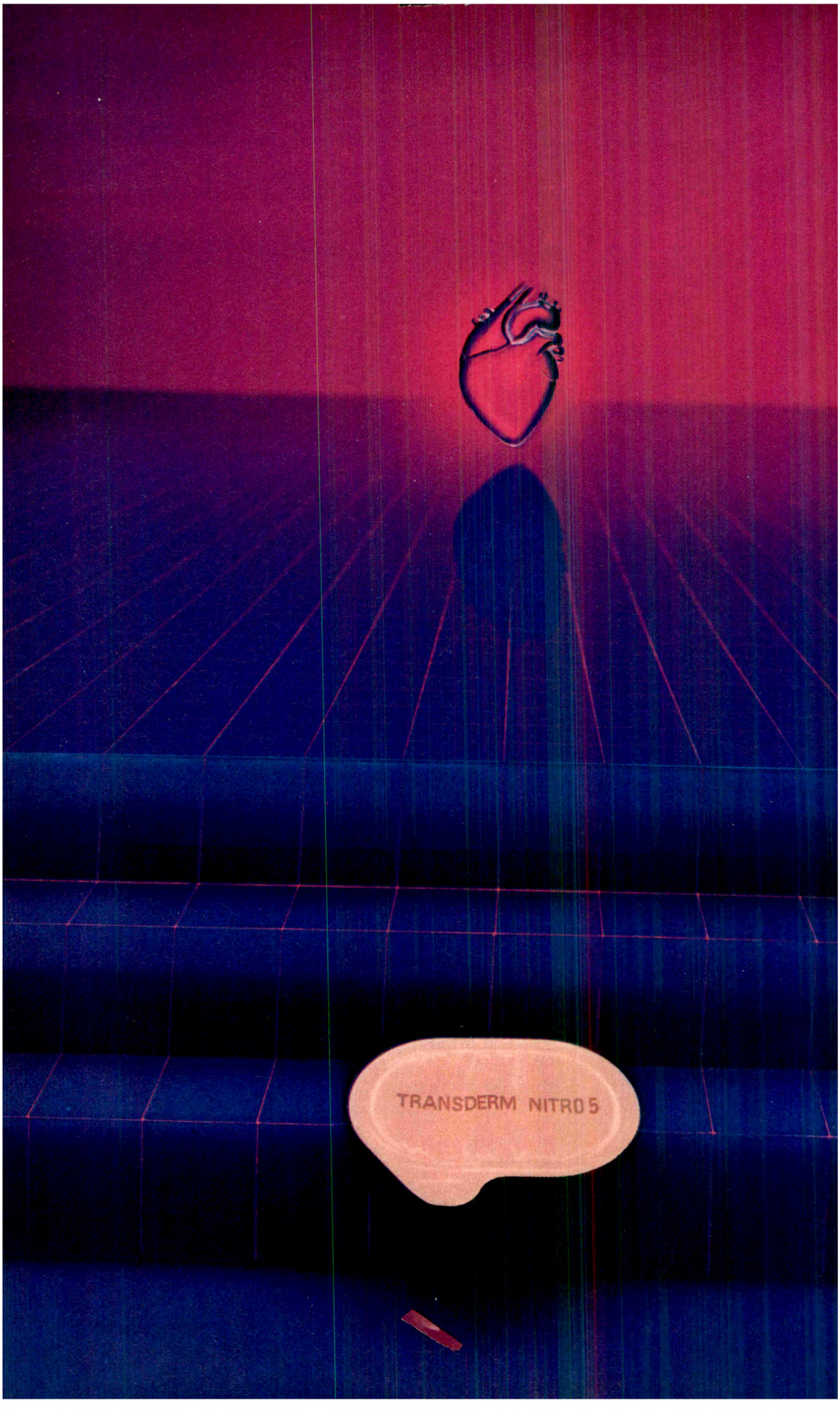
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nitroglycerin

Nitroglycerin—for more than 100 years the classic therapy for angina—now becomes more convenient, more simple, more practical.

First-step anginal prophylaxis

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A step ahead of long-acting oral nitrates

"Transdermal delivery of nitroglycerin . . . overcomes the inherent problems of the oral dosage forms regarding . . . bioavailability, convenience and compliance."*

24-hour sustained therapeutic blood levels of nitroglycerin.
In contrast, so-called long-acting oral nitrates must be given in repeated doses throughout the day.

Eliminates the first-pass effect.
Unlike oral nitrates, which are predominantly inactivated in the liver, transdermal nitroglycerin bypasses the liver and enters directly into systemic circulation.

Only one simple application a day.
Avoids the inconvenience of multiple dosages.

Small, cosmetically acceptable and well tolerated.
Will not leak or stain clothing. May even be worn while bathing or swimming. Few reports of skin irritation.

Note: Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

Black CD: Transdermal drug delivery systems. *US Pharmacist* 1982 (Nov), 7(11):49-78

Before prescribing, please read full Prescribing Information.

CIBA

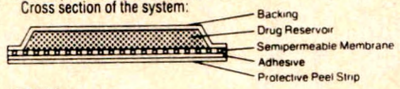
Transderm®-Nitro
(nitroglycerin)
Transdermal Therapeutic System

DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system: 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

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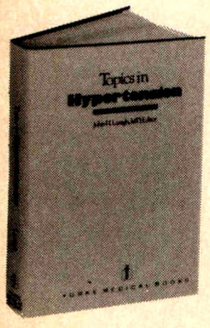

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PROGRAMALITH® AV

Programmable-Interrogatable™ Dual-chamber Pacing System-Model 223

(Except as noted, all data specified represent nominal values for a unit at standard values, measured at Beginning-of-Life, 100% pacing, 500 ohm load and 37° C.)

Nominal Pacing Rate	70 ± 1 ppm
Magnet Rate	90 ppm at Beginning-of-Life (BOL) 77 ppm at Recommended Replacement Time (RRT)
Interference Rate	Programmed Rate (70 ± 1 ppm)
Pulse Amplitude (leading edge)	5.3 V (BOL), 4.6 V (RRT)
Pulse Width	0.8 ms (BOL), 1.0 ms (RRT)
Inhibition Sensitivity to 50 Hz (20 ms) Haversine Signal	2.0 mV (positive or negative)
Refractory Period	325 ms
AV Interval (DVI Mode)	150 ms (105 ms with magnet applied)
Stimulating Energy	33 μjoules (BOL), 30 μjoules (RRT)

	VVI MODE	DVI MODE
Battery Current Drain:		
Inhibited	6 μAmps (16.8 μWatts)	6 μAmps (16.8 μWatts)
Pacing	23 μAmps (64.2 μWatts)	38 μAmps (106.9 μWatts)
Input Impedance	24 Kohms	

Programmable Parameters:	Rate, Pulse Amplitude, Pulse Width, Sensitivity, Refractory Period and Mode
Interrogation Functions:	
Programmed Parameter Status	All
With 398 Programmer:	
Vtr Lead Impedance	250-1990 ohms
Battery Impedance	1-50 Kohms
Battery Current Drain	5-100 μAmps
Measured Telemetry Values Retrieved Additionally with 398E Programmer:	Rate, Vtr. Pulse Current, Vtr. Pulse Voltage, Vtr. Pulse Energy, Vtr. Pulse Charge, Battery Voltage, A-V Delay
Programming Method	Pulsed Magnetic Energy in Conjunction with DC Magnetic Field. Unique "Error Screen" protects against phantom programming.
Print Mode	All Interrogatable Functions
Trace Mode	Step-by-Step Programming Procedure
Power Source:	
Chemistry	Lithium-Iodine
Capacity:	
Total	2.5 AH (7.00 WH)
Useful	1.93 AH (5.40 WH)
Voltage	2.8 V
Dimensions:	6.3 x 4.7 x 1.17 cm
Weight	68 gms
Volume	30 cc
Density	2.3 gm/cc (Approximately)
Hermetic Case	Titanium with Insulative Coating
Connector Material	Epoxy
Projected (theoretical) Life	9.6 years (VVI Mode)
Recommended Replacement Time:	
Magnet Rate Decrease	from 90 to 77 ppm
Pulse Width Increase	25%
Pacing Configuration:	223-dual unipolar

INDICATIONS The Pacesetter Model 223 Programalith® is a dual-chamber A-V sequential pacemaker specifically indicated for therapeutic control of conduction disorders requiring restoration of both rate and A-V synchrony. In the A-V sequential mode (DVI), the Model 223 has application for patients with extensive myocardial infarction with A-V block and sinus bradycardia. The Model 223 may also be programmed for single-chamber pacing in either ventricle or atrium.

CONTRAINDICATIONS Medical literature indicates no known contraindications to the use of pacemakers as a therapeutic means for heart-rate control. However, sequential atrial-ventricular pacing modes are contraindicated in the presence of atrial flutter and fibrillation.

WARNINGS Although special shielding and filters protect Pacesetter Pulse Generators against defibrillation pulses of up to 400 Watt seconds, defibrillator paddles should not be placed near the pulse generator and pacer function should be verified following defibrillatory charges. Caution should be exercised also with diathermy and electrosurgical units which produce high field strength signals, possibly resulting in suppression of the device's output, reversion to asynchronous mode and/or overheating of the metallic components. Pulse generators must not be sterilized by steam autoclaving or gamma radiation nor cleaned ultrasonically.

PRECAUTIONS Physicians should be aware that any pulse generator will ultimately cease to function from battery depletion and may fail at any time owing to random malfunction. Pacesetter Pulse Generators have been designed so that the average life of the circuitry will greatly exceed the expected life of the power source. As all critical circuitry and the battery are hermetically sealed, the package is virtually unaffected by the body environment; therefore, the longevity is determined almost entirely by the battery. Insufficient time has passed to completely determine various factors that may affect the life expectancy of the present battery configurations. Thus any estimates of pulse generator longevity must be based on theoretical projections of available date, principally accelerated test data, as well as expected pacing characteristics. Recommended replacement times, indications for end-of-life and longevity factors are discussed thoroughly in Pacesetter's appropriate physicians' manual for the unit to be implanted and should be consulted prior to implantation.

POTENTIAL COMPLICATIONS & SIDE EFFECTS Lead displacement/fracture, cardiac tamponade, muscle or nerve stimulation, embolism, infection, erosion of lead or pulse generator through skin and body rejection phenomena are possible.

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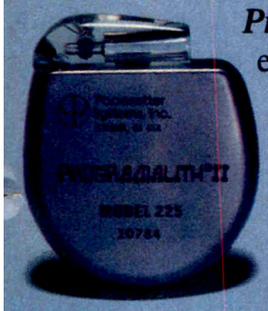

Programalith® II has established its own virtually unequalled cumulative survival record of 99.7% since January 1982. Its smaller, more physiologic configuration, thinness and theoretical longevity of greater than 8 years are combined with six-parameter multi-programmability and bi-directional telemetry features.

Programalith® A-V is a multi-modal, multi-programmable, dual-chamber A-V sequential pacemaker, incorporating extensive programmed and measured telemetry data.

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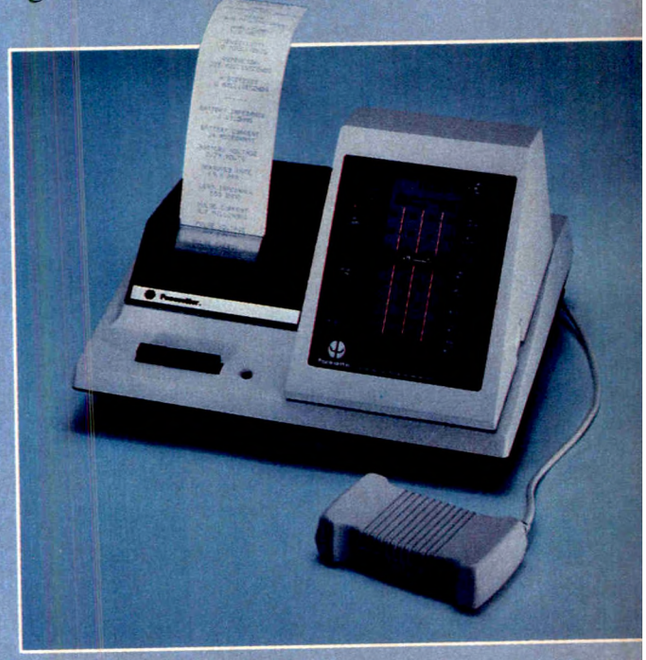
The Pacesetter® Model 398E Programming/Telemetry System.
Multi-programmability up to six parameters; extensive programmed and measured telemetry data capable of advising physicians both what the pacing system *should* be doing as well as what it is *actually* doing.



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65
hours
mean half-life
(N_1-desalkyl
flurazepam)
Some benzodiazepine hypnotics have too long a half-life
Too long a half-life may lead to:
• drug accumulation
• hangover/daytime drowsiness
• interaction with other agents
Some benzodiazepine hypnotics have too short a half-life
Too short a half-life may lead to:
• nocturnal awakenings
• early-morning awakenings
• anterograde amnesia
3
hours
mean half-life
(triazolam)
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Restful sleep, alert awakening

RESTORIL®

15 mg
30 mg
capsules

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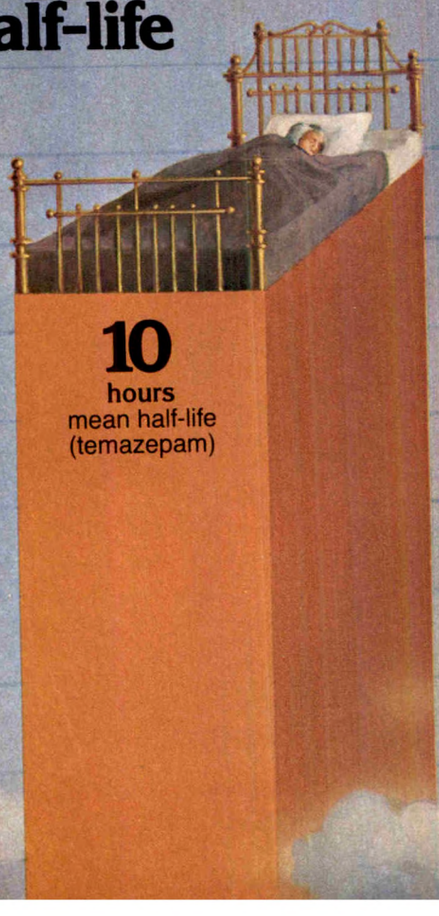

A half-life (mean of 10 hours)
that parallels normal sleep time:

- patient gets 7-8 hours sleep
- most medication gone by morning
- patient awakes alert and refreshed
- minimal side effects
- insignificant accumulation

Please see brief summary of prescribing information on next page.

Restful sleep,
alert awakening

RESTORIL®

C IV
15 mg
30 mg
capsules

(temazepam)

A more appropriate half-life

One 30-mg capsule, h.s.—*usual adult dosage.*
One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tesis: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

DOSAGE AND ADMINISTRATION: *Adults:* 30 mg usual dosage before retiring; 15 mg may suffice in some. *Elderly and/or debilitated:* 15 mg recommended initially until individual response is determined.

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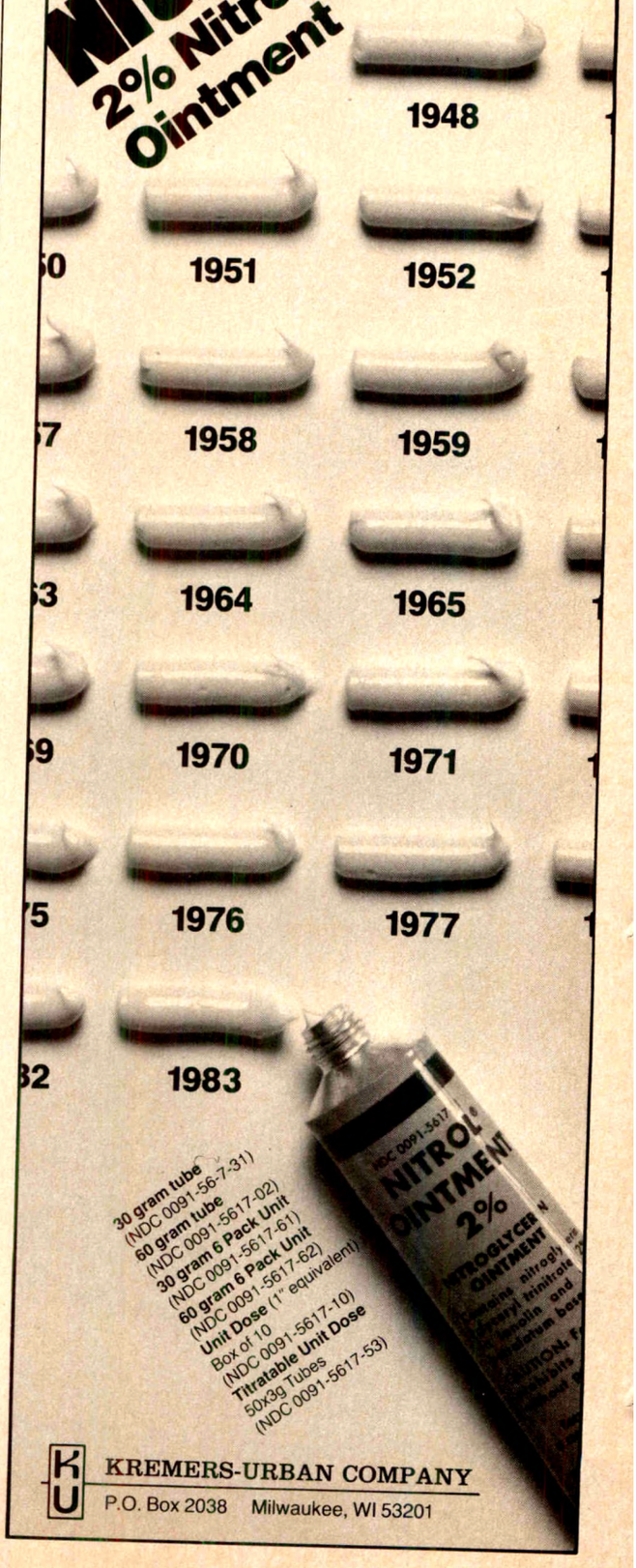

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First Ultra-Short–Acting Beta-Adrenergic Blocking Agent: Its Effect on Size and Segmental Wall Dynamics of Reperfused Myocardial Infarcts in Dogs

RÜDIGER LANGE, MD, ROBERT A. KLONER, MD, PhD, and EUGENE BRAUNWALD, MD

Beta-adrenergic blocking agents have an established role in the treatment of myocardial ischemia, but precipitation of cardiac failure or bronchospasm may restrict their use in some patients with acute myocardial infarction or in those undergoing coronary bypass surgery. ASL-8052 is a new cardioselective ultra-short–acting beta blocker which allows abolition of beta blockade within 16 minutes on termination of an intravenous infusion. An investigation was made of the effect of ASL-8052 on myocardial infarct size, regional myocardial wall function, and hemodynamic features during a 3-hour experimental occlusion of the left anterior descending coronary artery followed by 3 hours of reperfusion in dogs.

Twenty-two dogs (10 control, 12 treated) were instrumented for the measurement of left ventricular (LV) pressure, the first derivative of left ventricular pressure (LV dP/dt), systolic and diastolic aortic pressure, and heart rate. Two pairs of ultrasonic crystals were inserted into a nonischemic segment and an ischemic marginal zone segment to obtain percent segment shortening. The area of necrosis was determined by tetrazolium staining and expressed as a percentage of the in vivo area at risk obtained by autoradiography. Dogs in the control group received saline solution; in treated dogs, a continuous infusion of ASL-8052 was begun 15 minutes after occlusion with a dose "titrated" to reduce the heart rate by approximately 20% (100 to 150 μg/kg/min). After 3 hours of reperfusion, the amount of myocardial tissue necrosis, as a function of the in vivo area at risk, was significantly lower in ASL-8052–treated (48 $\pm$ 7%) than in control (73 $\pm$ 6%) dogs ($p < 0.025$). Upon reperfusion, segment shortening decreased in control dogs from $-3.3 \pm 1.1\%$ after 3 hours of occlusion to $-6.3 \pm 1.9\%$ ($p < 0.05$) 2 hours after reperfusion (that is, systolic bulging increased). This functional deterioration upon reperfusion did not occur in treated dogs. During the occlusion period, infusion of ASL-8052 caused a decrease in heart rate of 22 $\pm$ 3% ($p < 0.001$) and in LV dP/dt by 22 $\pm$ 4% ($p < 0.05$). Upon reperfusion, control dogs had an increase in heart rate of 26 $\pm$ 1% ($p < 0.05$). In treated dogs, heart rate did not change. Hence, infarct size, reperfusion tachycardia, and myocardial wall asynergy were reduced in ASL-8052–treated dogs. A potential advantage of this agent is that its short duration of action would allow rapid reversal of beta blockade if adverse effects developed.

Beta-blocking agents have an established place in the treatment of myocardial ischemia; in some studies they have been shown to reduce the size of an experimentally induced myocardial infarct (MI)[1,2] and to reduce long-term mortality in patients with acute MI.[3] However, fear of adverse effects, particularly precipitation of cardiac failure, bronchospasm, bradycardia, and atrioventricular block, has restricted the use of beta blockers in patients with acute MI or in those undergoing cardiac surgery who have a history of left ventricular dysfunction, pulmonary disease, or atrioventricular conduction delay. The relatively long duration of action of available beta blockers restricts the flexibility of their use in such patients. ASL-8052 is a new cardioselective beta-adrenergic antagonist without intrinsic sympathomimetic activity, which has an extremely brief duration of action believed to be due to rapid metabolic degradation by serum and tissue esterases[4] (Fig. 1). ASL-8052 is administered by continuous infusion and the dose is "titrated" in order to achieve any desired level of blockade. The potential advantage of this drug over available beta blockers is that, should adverse effects ensue from its administration, beta blockade can be rapidly terminated upon discontinuation of the infusion.

From the Department of Medicine, Harvard Medical School, and Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by Grants HL 23140 and SCOR 26215 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland; by a grant from the American Critical Care Corporation, McGaw Park, Illinois; and by funds contributed in part by the Massachusetts Heart Association, Boston, Massachusetts. Manuscript received November 29, 1982; revised manuscript received March 9, 1983, accepted March 12, 1983.

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In patients, early coronary revascularization can seldom be initiated before 3 to 4 hours after the onset of chest pain. Since there is evidence that beta blockade can delay cell death before reperfusion,[2] it was of interest whether this mode of treatment, in conjunction with reperfusion, could reduce ultimate infarct size.

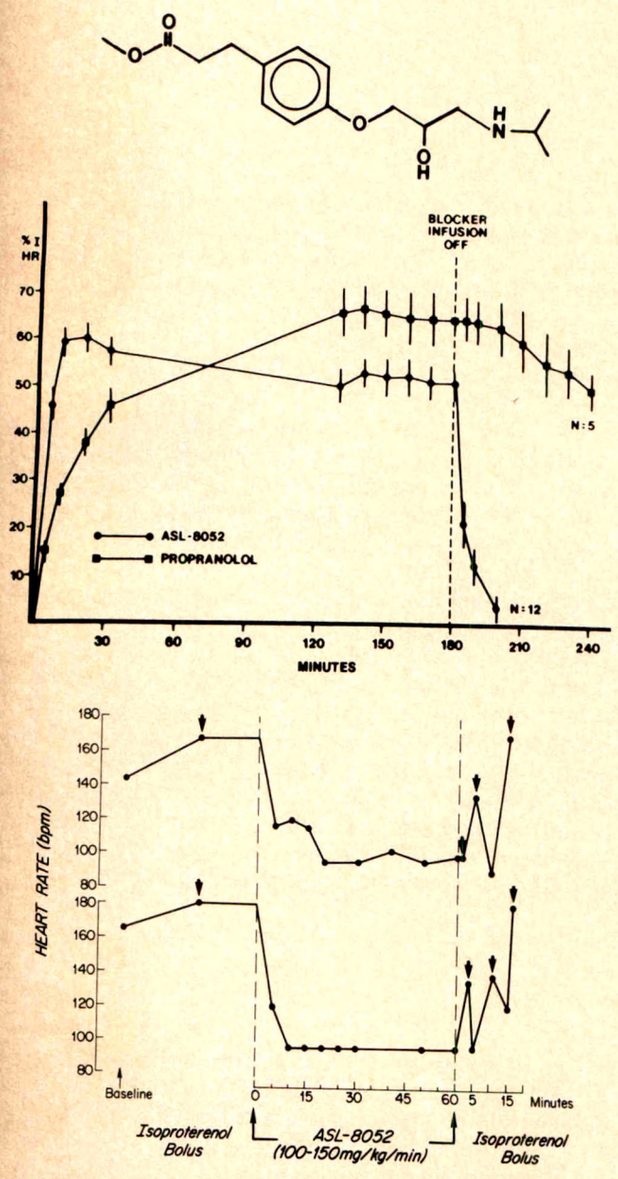

FIGURE 1. Top, molecular structure of ASL-8052. **Middle,** time course of beta blockade during and after constant infusion of ASL-8052 (50 μg/kg/min) and propranolol (1.13 μg/kg/min) in dogs. Graph shows percent inhibition (%I) of heart rate (HR) response to isoproterenol boluses (0.5 μg/kg) on the ordinate over time on the abscissa. Isoproterenol bolus doses were administered at 10-minute intervals before, during, and after a 3-hour intravenous infusion of ASL-8052. The time required for 80% recovery from beta blockade was only 12 ± 3 minutes in the group receiving ASL-8052. (Reprinted with permission from Zaroslinski et al, Life Sciences 1982; 31(9):899–907). **Bottom,** heart rate response to bolus doses of isoproterenol in 2 dogs that we subjected to a 60-minute continuous ASL-8052 infusion. Sixteen minutes after the termination of the infusion the HR response to bolus doses of isoproterenol was 100% of the preinfusion response and hence beta blockade was considered to be reversed.

However, under these circumstances the depression of function of nonischemic myocardium by the persistent action of conventional beta blockers could be potentially undesirable. The specific objective of the present study was to determine the effects of a continuous infusion of ASL-8052 on myocardial infarct size, regional myocardial wall function, and hemodynamic function during a temporary 3-hour coronary artery occlusion followed by reperfusion.

Methods

Preparation: Twenty-nine mongrel dogs of either sex weighing 11 to 23 kg were anesthetized with sodium thiamylal (30 mg/kg), intubated, and placed on a Harvard respirator. All dogs received an intravenous bolus dose of succinylcholine (40 mg/kg). The right femoral vessels were dissected free and catheters inserted. A thoracotomy was performed in the fifth left intercostal space, the heart was suspended in a pericardial cradle, and a small segment of the left anterior descending coronary artery was isolated. A micromanometer-tipped pressure transducer (Millar Instruments, Houston, Texas) was inserted into the left ventricle through a stab wound in the apex, and a polyethylene catheter was placed into the left atrium.

Regional function: Two pairs of miniaturized piezoelectric crystals (Dimonics, Boston, Massachusetts) (1.5 to 2 mm) functioning as emitters and receivers were implanted 10 to 20 mm apart into the epicardium through a small incision. One pair of crystals was placed in the upper part of the left anterior ventricular wall to measure nonischemic regional function. The other pair was placed toward a marginal border zone assessed by visual cyanosis, during a 5- to 10-second occlusion of the left anterior descending coronary artery as has been described previously by Theroux et al.[5] Both pairs were positioned perpendicularly to the major axis of the left ventricle. The epicardial location of the crystals was chosen to assess specifically the function of the myocardium presumed to have the best chance of being salvaged by reperfusion, that is, the epicardium at the edge of the ischemic zone. The position of the crystals was confirmed at necropsy. The dynamics of segment length changes were recorded on line by continuous measurement of ultrasonic transit time between the crystals. The measured transit time was calibrated in steps of 1 μs generated by a crystal controlled pulse generator.

In vivo area at risk and infarct size. The in vivo area at risk (AR) and the area of necrosis (AN) were determined by a method described previously.[6] Six hundred thousand human albumin microspheres labeled with technetium-99m (diameter 20 μm) (3M, Eagen, Minnesota) were injected into the left atrium 15 minutes after coronary occlusion. At the end of the experiment, the heart was excised and the left ventricle was sectioned into 4 mm thick slices. The slices were then incubated for 15 minutes in triphenyltetrazolium chloride at 37°C. Triphenyltetrazolium chloride stains normal tissue containing dehydrogenase enzymes brick red whereas infarcted tissue, depleted of these enzymes, remains pale yellow.[7] The slices were then exposed for 18 hours on an 8 × 10 in sheet of high speed x-ray film, and developed in an X-Omat (Kodak Medical Products, Rochester, New York) automatic processor. Normally perfused tissue appears as an area of high radiographic density on the final autoradiogram, whereas ischemic tissue appears as an area of low or absent radioactivity. This "in vivo" AR technique was chosen to reflect the physiologic conditions during coronary artery occlusion by taking into account collateral blood flow distribution as 1 major determinant of infarct size.

All slices were weighed and the inner and outer margins were traced on a clear acetate overlay. By superimposing the same tracing over the autoradiogram, the boundary of the ischemic area (in vivo AR) was drawn at the edge of the zone of decreased radiographic density by eye. The AN was traced on an acetate overlay. AN and AR were planimetered, expressed as a percentage of the total slice area, and calculated for weight in grams. By adding the weights for all slices, the total size of the infarct and the risk region were obtained as absolute weight and as percentage of total left ventricle. The AN as a percentage of the AR was calculated by: AN/AR × 100.

Regional myocardial blood flow: To assess regional myocardial blood flow, approximately 2.0×10^6 radioactive microspheres labeled with either scandium-46, tin-113, or cerium-141 were injected into the left atrium and a reference blood sample was drawn from the femoral artery over a 90-second period at 15.3 ml/min. For tissue counting, sections from 4 different zones were cut from 2 representative heart slices; these were divided into epicardial and endocardial halves: zone 1, the central ischemic zone; zone 2, the zone within the lateral portion of the AR cut according to the acetate overlay tracing; zone 3, the zone approximately 5 mm outside the AR; and zone 4, the zone remote from the AR in normally perfused tissue.

Dissected pieces were weighed and blood flows were calculated as previously described.[8]

Experimental Measurements and Protocol

Left ventricular systolic pressure was recorded from the micromanometer tipped pressure transducer which had been calibrated before the experiment. Aortic pressure and left atrial pressure were obtained through fluid-filled catheters connected to a Statham P23Db pressure transducer. LV dP/dt was obtained by electronic differentiation. Lead aVF of the electrocardiogram was monitored and was used to calculate heart rate. From the recorded signals of the ultrasonic dimension gauges, the end-diastolic length (EDL) and end-systolic length (ESL) were identified by the beginning of the rapid increase in left ventricular pressure just before the isovolumetric contraction and the peak negative first derivative of left ventricular pressure respectively. Percent segment shortening (% SS) was calculated from the following formula: % SS = (EDL − ESL)/EDL ×100.

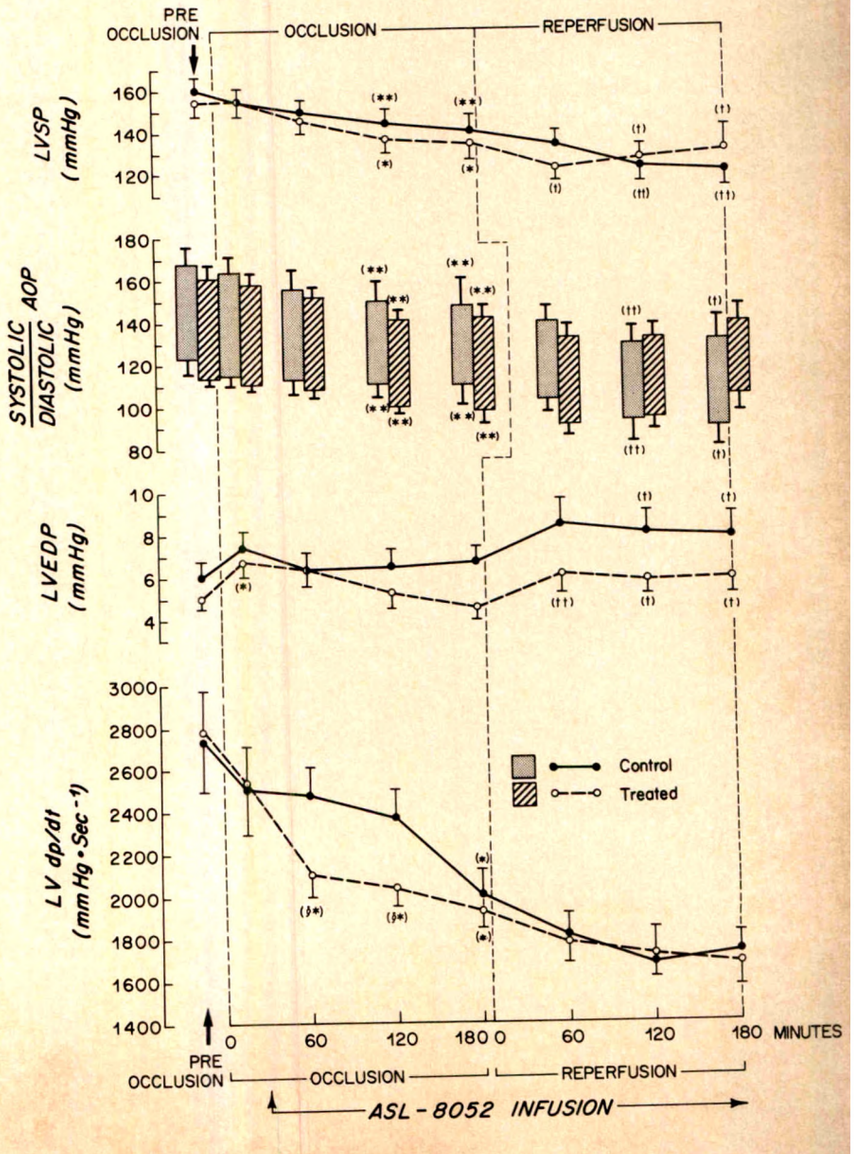

FIGURE 2. Top, left ventricular systolic pressure (LVSP), systolic and diastolic aortic pressure (AoP), and left ventricular end-diastolic pressure (LVEDP) in control and treated dogs. **Bottom,** rate of increase of left ventricular pressure (LV dP/dt). ASL-8052–treated dogs show significantly lower LV dP/dt values during the occlusion period. * $p < 0.025$ compared with preocclusion value; ** $p < 0.001$; † $p < 0.05$ compared with 180 minutes after occlusion value; ‡ $p < 0.025$; § $p < 0.05$ compared with corresponding value in control group.

All animals received an intravenous bolus dose of 1.5 mg/kg of lidocaine immediately after left anterior descending coronary artery occlusion. At 10, 60, and 240 minutes after occlusion, microsphere injections into the left atrium were performed for determination of regional myocardial blood flow. Albumin microspheres for autoradiography were injected into the left atrium 15 minutes after coronary occlusion. Immediately thereafter a continuous infusion of either saline solution (10 dogs) or of the ultra-short-acting beta blocker ASL-8052 (12 dogs) was started and continued until the termination of the experiment. The dose of ASL-8052 ranged from 100 to 150 μg/kg/min and was adjusted in order to reduce heart rate by approximately 20% of the preocclusion value. The infusion rate of ASL-8052 was then held constant. The coronary occlusion was released after a 3-hour period of ischemia which was followed by 3 hours of reperfusion. These time periods were chosen because of their relevance to patients undergoing early fibrinolytic or surgical revascularization.

Results

A total of 29 dogs were studied. In 2 dogs, the pharmacologic properties of ASL-8052 were investigated without coronary artery occlusion. Five dogs were excluded from the study, 4 because of ventricular fibrillation during the first 15 minutes after coronary artery occlusion and 1 because of the high coronary collateral flow which prevented the development of sufficient ischemia to produce epicardial cyanosis. Of the 22 remaining dogs, 10 were assigned to the control and 12 to the treated group.

Beta blockade by ASL-8052: Preliminary experiments were designed to confirm previous reports about the short duration of action of ASL-8052[4] (Fig. 1 middle). Two dogs were instrumented as described above but coronary artery occlusion was not carried out. An intravenous bolus dose of isoproterenol (0.5 μg/kg) resulted in an increase in heart rate of 10 to 15%. After the heart rate had returned to baseline, ASL-8052 was infused for 60 minutes at a dosage of 100 to 150 μg/kg/min. Five minutes after the initiation of the ASL-8052 infusion, the heart rate was about 20% below the preinfusion value; it remained there during the infusion period. After discontinuation of the infusion, the attenuation of the ASL-8052 pharmacologic action was determined by examining the response to bolus doses of isoproterenol (0.5 μg/kg). Sixteen minutes after discontinuation of the infusion, the heart rate response was 100% and the LV dP/dt response was 92% of the preinfusion response to isoproterenol; hence, beta blockade was considered reversed (Fig. 1 bottom).

Hemodynamic changes (Fig. 2): Hemodynamic changes immediately upon occlusion were not significantly different from preocclusion value in either group. At 120 minutes and 180 minutes after occlusion left ventricular systolic pressure, as well as aortic systolic and diastolic pressures, were significantly lower than preocclusion values in both the control (saline solution-treated) and ASL-8052–treated group ($p < 0.05$). Sixty minutes after occlusion, or 45 minutes after the

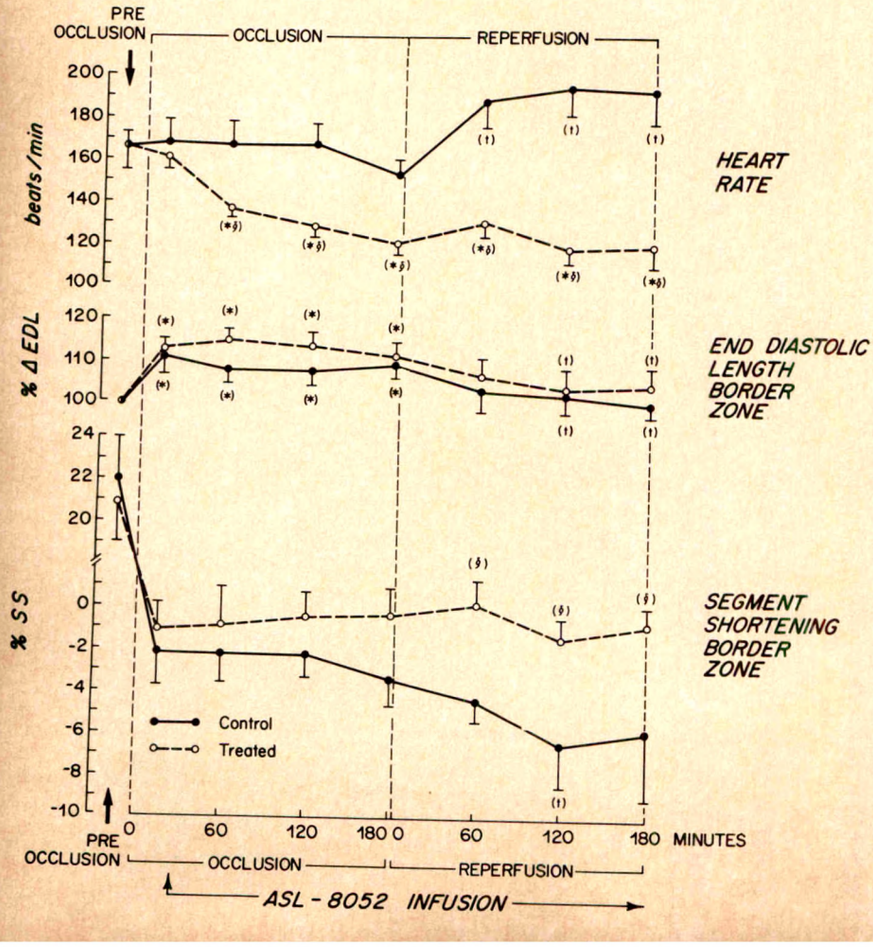

FIGURE 3. Top, heart rate in ASL-8052–treated and control dogs. Percent change in end-diastolic length (Δ%EDL) **(center)** and percent segment shortening (% SS) **(bottom)** in the ischemic "border zone." * $p < 0.001$ compared with preocclusion value; § $p < 0.025$ compared with corresponding value in control group; † $p < 0.05$ relative to 180 minutes after occlusion value.

TABLE I Changes in End-Diastolic Length (Δ%EDL) Expressed as a Percentage of Preocclusion Baseline and Percent Segment Shortening (% SS)

		Occlusion (min)				Reperfusion (min)		
	Preocclusion	15	60	120	180	60	120	180
Nonischemic Segments								
% ΔEDL								
Control	100	107 ± 3*	105 ± 5*	106 ± 4*	106 ± 3*	107 ± 3	105 ± 3	104 ± 2
Treated	100	107 ± 2*	105 ± 2*	104 ± 1*	104 ± 2*	101 ± 2†	101 ± 2†	102 ± 2
% SS								
Control	13 ± 2	15 ± 3	15 ± 2	15 ± 3	13 ± 2	14 ± 2	13 ± 2	12 ± 1
Treated	13 ± 2	16 ± 2	15 ± 1	15 ± 1	14 ± 1	13 ± 1	14 ± 1	13 ± 1
Border Zone Segments								
% ΔEDL								
Control	100	112 ± 3*	108 ± 3§	108 ± 3§	111 ± 3§	104 ± 5	103 ± 4†	101 ± 4†
Treated	100	113 ± 2*	115 ± 3*	114 ± 3*	112 ± 3*	108 ± 4	105 ± 5†	106 ± 5†
% SS								
Control	22 ± 2	−2 ± 2§	−2 ± 1§	−2 ± 1§	−3 ± 1§	−4 ± 1§	−6 ± 2†§	−6 ± 2§
Treated	21 ± 3	−1 ± 1§	−1 ± 1§	−1 ± 1§	−1 ± 1§	1 ± 1§‖	−1 ± 1§‖	−1 ± 1‡§

Values are mean ± standard error.
* Significantly ($p < 0.05$) different compared with preocclusion value (§ $p < 0.001$).
† Significantly different compared with 180 minute value ($p < 0.05$).
‡ Significantly different compared with value at comparable time in control group ($p < 0.05$) (‖ $p < 0.025$).

initiation of either ASL-8052 or saline solution infusion, LV dP/dt in the treated group had decreased to 78 ± 4% of the preocclusion value ($p < 0.05$ compared with preocclusion baseline). In contrast, in the saline solution-treated controls, LV dP/dt did not decrease within the first 2 hours of coronary artery occlusion and was significantly ($p < 0.05$) higher than in the beta-blocked group. During the third hour after occlusion, LV dP/dt values also decreased in the control group and approached those observed in the treated group. Adjusting the beta-blocking agent according to heart rate resulted in an 18 ± 3% decrease in this parameter below preocclusion values ($p < 0.001$) 60 minutes after occlusion (Fig. 3). The infusion rate of the beta blocker was then held constant. Heart rate showed no change in the saline solution-treated controls during the 3 hours of occlusion, and was hence significantly ($p < 0.025$) lower in the ASL-8052–treated animals.

On reperfusion, LV systolic pressure as well as aortic systolic and diastolic pressures and LV dP/dt decreased. Left ventricular end-diastolic pressure increased both in control and treated animals (Fig. 2). Saline solution-treated dogs showed a significant increase in heart rate, from 153 ± 8 at the end of the occlusion period to 189 ± 12 after 60 minutes of reperfusion ($p < 0.05$) (Fig. 3). This reflected the occurrence of reperfusion arrhythmias, which included sinus tachycardia, ventricular tachyarrhythmias, and multifocal premature ventricular contractions. In 2 control dogs, however, sinus rhythm was maintained during the entire reperfusion period, suggesting that arrhythmias are frequently but not invariably associated with reperfusion. Heart rate in treated dogs during reperfusion was significantly lower than in control dogs ($p < 0.025$) (Fig. 3).

In summary, in contrast to control dogs, treated animals had a decrease of approximately 20% in heart rate and in LV dP/dt upon ASL-8052 infusion. During reperfusion, the 2 groups exhibited important differences in heart rate, which increased 25% above the occlusion level in saline solution-treated animals and did not change significantly in treated dogs.

TABLE II Values for Area at Risk and Area of Necrosis as Percentage of Total Left Ventricle and Area of Necrosis as Percentage of the Area at Risk

	Control (n = 10)	Treated (n = 12)	p
Area at risk (%LV)	23 ± 2	23 ± 2	NS
Areas of necrosis (%LV)	18 ± 3	11 ± 2	NS
Areas of necrosis/ area at risk ×100	73 ± 6	48 ± 7	$p < 0.025$

Values are mean ± standard error.
NS = not significant.

Regional function (Table I): In the nonischemic zone, end-diastolic segment length increased after occlusion, by 7% in both groups ($p < 0.05$ compared with preocclusion baseline). In the border zone segments, end-diastolic length increased by 12 ± 3% in the control group ($p < 0.01$ compared with preocclusion) and 13 ± 2% ($p < 0.05$) in the treated group. During the 3-hour occlusion period, the end-diastolic length in both the nonischemic and border zone segments remained elevated but returned to preocclusion levels upon reperfusion in both groups (Fig. 3). Segment shortening in the nonischemic segments was elevated in all animals during occlusion, indicating compensatory hyperkinesia. The initial response to coronary artery occlusion in the ischemic border zone was a change from active shortening to passive systolic lengthening in most dogs. Two control and 3 treated animals retained residual shortening of 3 to 6% and 1 dog in each group had an akinetic border zone segment. Since systolic bulging was predominant in both groups, the mean values for segment shortening at 15 minutes after occlusion, that is, just before treatment, were negative (Fig. 3).

During reperfusion the border zone segments of the saline solution-treated animals exhibited marked de-

terioration so that the mean segment shortening decreased from −3.3 ± 1.1% 180 minutes after occlusion to −6.3 ± 1.9% after 120 minutes or reperfusion ($p < 0.05$). In treated animals, this functional deterioration did not occur; 2 of the 12 treated dogs even demonstrated minimal systolic shortening presumably due to hyperemia during the early reperfusion period. Thus, reperfusion caused a significant increase in paradoxical systolic bulging in the border zone of the saline solution-treated animals, which was not observed in the dogs treated with the beta blocker (Fig. 4). The differences in segment shortening between the 2 groups were significant at 60 ($p < 0.01$), 120 ($p < 0.025$), and 180 ($p < 0.05$) minutes after the onset of reperfusion.

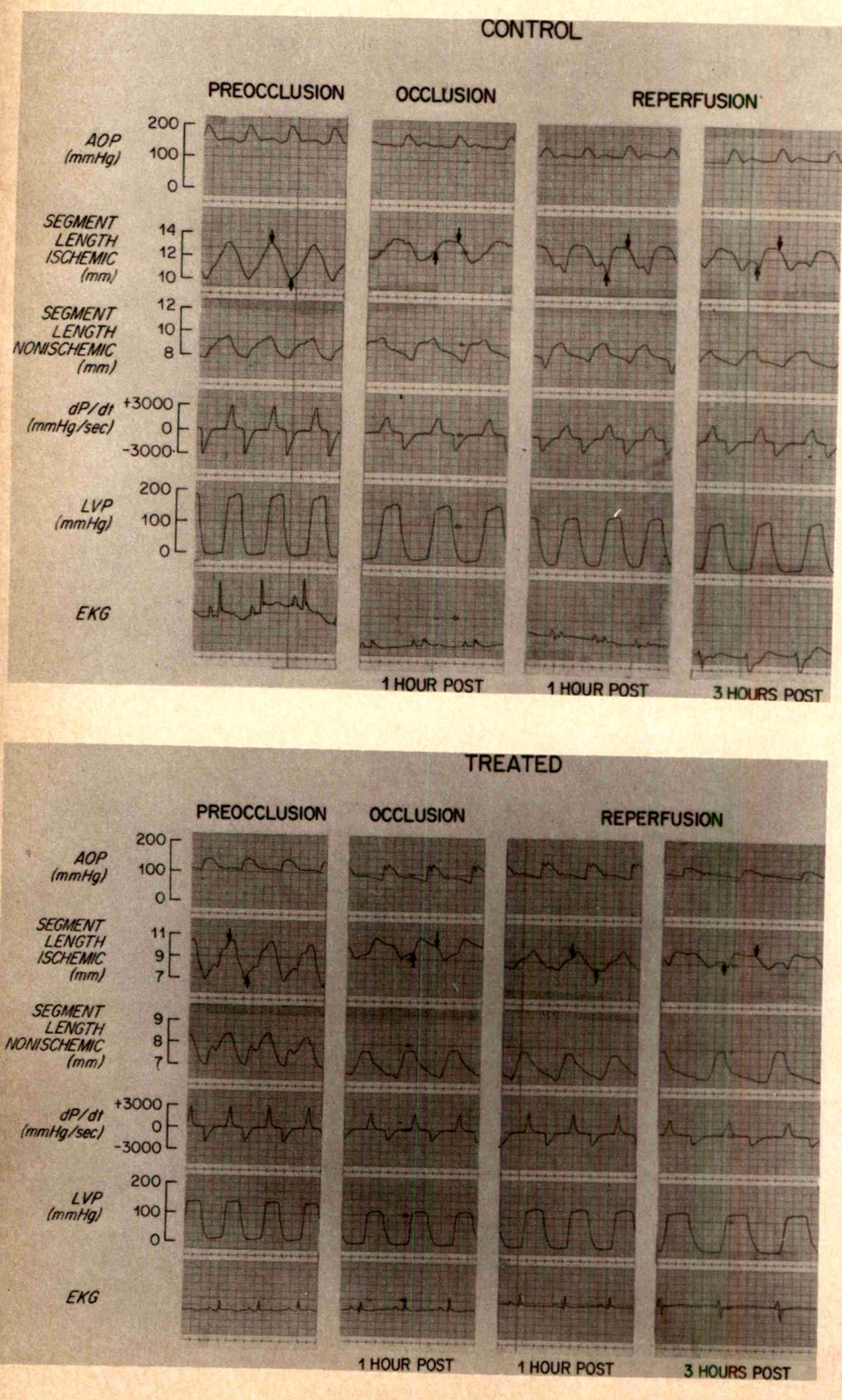

FIGURE 4. Tracings of ischemic ("border zone") and nonischemic segment length, aortic pressure (AoP), dP/dt, left ventricular pressure (LVP), and electrocardiogram (EKG). The control animal shows increased systolic paradoxical bulging (**arrows**) 1 and 3 hours after reperfusion (**top**). The ASL-8052–treated dog shows some contraction (**arrows**) 1 hour after occlusion which is however not maintained throughout the reperfusion period (**bottom**).

TABLE III Epicardial (EPI) and Endocardial (ENDO) Blood Flow (ml/g/min)

	ZONE 1		ZONE 2		ZONE 3		ZONE 4	
	EPI	END	EPI	END	EPI	END	EPI	END
10 minutes after occlusion								
Control	0.24 ± 0.11	0.13 ± 0.06	0.31 ± 0.10	0.27 ± 0.10	1.31 ± 0.20	1.22 ± 0.15	1.55 ± 0.21	1.46 ± 0.15
Treated	0.22 ± 0.07	0.17 ± 0.05	0.50 ± 0.16	0.44 ± 0.16	1.47 ± 0.23	1.41 ± 0.21	1.71 ± 0.20	1.83 ± 0.19
60 minutes after occlusion								
Control	0.36 ± 0.13	0.17 ± 0.09	0.49 ± 0.19	0.34 ± 0.13	1.35 ± 0.17	1.23 ± 0.17	1.67 ± 0.23	1.58 ± 0.17
Treated	0.42 ± 0.12	0.14 ± 0.04	0.65 ± 0.14	0.39 ± 0.10	1.46 ± 0.13	1.34 ± 0.14	1.65 ± 0.14	1.61 ± 0.18
60 minutes after reperfusion								
Control	0.90 ± 0.15	0.69 ± 0.10	0.91 ± 0.12	0.79 ± 0.10	1.13 ± 0.08	1.00 ± 0.05	0.96 ± 0.09	1.00 ± 0.05
Treated	1.44 ± 0.24	1.18 ± 0.24	1.47 ± 0.23	1.27 ± 0.21	1.23 ± 0.12	1.18 ± 0.13	1.25 ± 0.16	1.19 ± 0.18

Values are mean ± standard error.

Infarct size (Table II): The AR defined by autoradiography was similar in both groups. In control animals, 73 ± 6% of the ischemic AR became necrotic while only 48 ± 7% became necrotic in treated animals ($p < 0.025$) (Fig. 5). Examination of the autoradiograms and the triphenyltetrazolium chloride-stained slices of the left ventricle revealed that in control dogs the salvaged myocardium, that is, the tissue that was ischemic but did not progress to necrosis, was generally subepicardial in location.

There was an inverse correlation between the quantity of myocardial necrosis, expressed as a percentage of the AR, and subepicardial regional myocardial blood flow within this area ($r = -0.60$ control; $r = -0.90$ treated) (Fig. 6). The regression line for the treated group is significantly ($p < 0.01$) displaced downwards compared with that of the control dogs, suggesting that there was less necrosis per given blood flow.

Regional myocardial blood flow (Table III): Ten minutes after occlusion, blood flow in the central ischemic zone was 10 to 15% of that in the normal zone with a generally greater reduction of flow in the subendocardium. In both groups there was a tendency to blood flow redistribution with time, with flow increasing in the subepicardium at the expense of that in the subendocardium. Throughout the study flows in treated animals were not different from control dogs.

Discussion

The present investigation yielded 2 major results. First, after a 3-hour occlusion of the left anterior descending coronary artery followed by 3 hours of reperfusion, myocardial tissue necrosis expressed as a function of the in vivo AR was significantly lower in dogs treated with an ultra-short–acting beta blocker than in saline solution-treated control dogs. Second, in comparison with saline solution-treated controls, in dogs treated with this agent, the extent of paradoxical systolic expansion of the border zone segment did not increase upon reperfusion. Also during reperfusion, dogs treated with the beta blocker did not develop the ventricular tachyarrhythmia observed in control dogs.

The potential of beta-blocking agents to reduce infarct size both in experimental animals and in patients has been studied extensively; although a number of investigators have reported favorable effects,[1,2,9,10] the

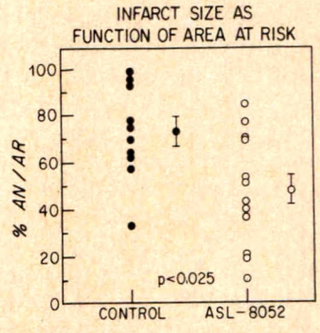

FIGURE 5. Area of necrosis (AN) by tetrazolium staining as a function of the "in vivo" area at risk (AR) by autoradiography.

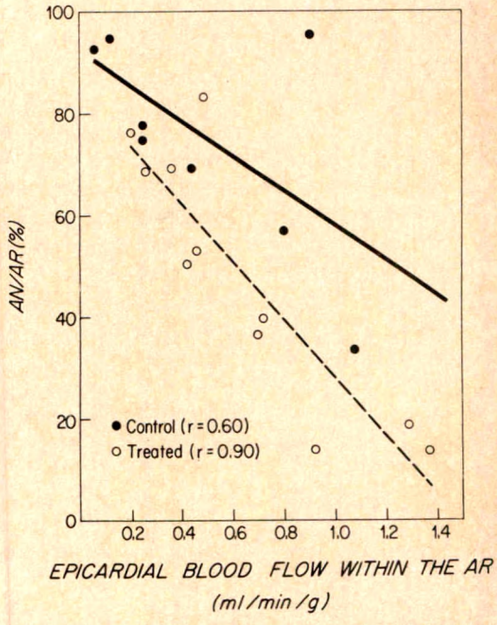

FIGURE 6. Regression lines correlating infarct size (AN/AR [%]) with subepicardial blood flow ($r = -0.60$ control; $r = -0.90$ treated). Comparison of the 2 lines indicates that infarct size is lower in the treated group than in the control group for any given blood flow. The 2 lines are $y = 91.78 - 33.63x$ (control) and $y = 85.77 - 57.45x$ (treated). The *t* test for equal slopes is not significant ($t = 1.26$, $df = 15$, not significant). Assuming that the lines are parallel, the regression lines are $y = 98.69 - 47.73x$ (control) and $y = 79.45 - 47.73x$ (treated). The test for equal intercept is $t = 2.64$ ($p < 0.01$).

results have not been uniform and a substantial number of studies have in fact shown no beneficial results.[11–13] A recent study by Reynolds et al[2] suggested that beta blockers may only be capable of delaying necrosis, and hence are only beneficial in a reperfusion model.

Several modes of action could be responsible for the reduction in infarct size by ASL-8052 in the present study. There is general agreement that infarct size is determined by the quantity of coronary collateral blood flow,[14] the size of the occluded coronary vascular bed,[11] myocardial oxygen consumption,[15] and the duration of coronary artery occlusion.[16] Since the quantity of coronary collateral flow as assessed by microspheres, the risk region as assessed by autoradiography, and the duration of occlusion were the same in control and ASL-8052–treated dogs, it appears likely that the reduction of myocardial oxygen requirements by beta blockade[13,15] was responsible for the reduction of infarct size. ASL-8052 caused a significant reduction in heart rate and LV dP/dt, both of which are important determinants of myocardial oxygen consumption.[15]

Regional function: Before occlusion the values for segment shortening were slightly lower in the nonischemic segments than in the border zone segments in both groups, because the nonischemic segments were located closer to the heart bases and therefore contracted less than the border zone segments which were in a more contractile mid-ventricular area. Both saline solution- and ASL-8052–treated dogs showed comparable levels of compensatory hyperfunction of nonischemic segments during the occlusion period. In contrast, Vatner,[17] Theroux,[5] and their co-workers reported that propranolol depressed regional contractility assessed by ultrasonic crystals in the nonischemic zone in closed-chest conscious dogs subjected to coronary artery occlusion. However, Theroux[18] did not find depression of nonischemic segments of myocardium by propranolol in anesthetized open-chest dogs, which is consistent with our results. Hence, the dose of the ultra-short–acting beta blocker which achieved salutory results in terms of infarct size reduction and performance of ischemic myocardium did not depress the performance of the nonischemic myocardium.

A surprising finding was the deterioration of function as expressed as increased systolic bulging of the border zone segment during reperfusion in the control group (Fig. 3 and 4). Delayed recovery of myocardial wall function after institution of reperfusion assessed by strain gauges[19] and ultrasonic crystals[20] has been reported after coronary artery occlusion. In the present study, systolic bulging, expressed as a percentage of end-diastolic length, increased in control dogs. Presumably, the myocardium at the edge of the ischemic zone, in which the crystals were placed, consists of cells with varying degrees of ischemic damage. In the untreated group these cells may have been further damaged and their residual contraction may have ceased during reperfusion, perhaps as a consequence of calcium influx and resultant mitochondrial damage and ischemic contracture. In the treated group this reperfusion injury might have been prevented because the cells were less damaged at the time reperfusion was begun.

Clinical implications: The results of this study suggest that ASL-8052 may be a potentially useful agent in the early treatment of patients with acute MI who are to undergo early revascularization, either thrombolytic or surgical. Rapid degradation of ASL-8052 by tissue and serum esterases permits cessation of beta blockade within minutes of discontinuation of a continuous infusion or a reduction in blockade with a lowering of the dose. This offers a potential clinical advantage over standard beta blockers, which have a much longer duration of action, since it is not possible to "back off" when the dose is too high and the natural temptation of the clinician is to err on the side of administering a safe, but possibly ineffective dose.

In view of the brief duration of action of ASL-8052, this drug could be used in clinical practice to reduce myocardial oxygen consumption maximally; the hazard of serious depression of cardiac function which accompanies persistent beta blockade is reduced since the drug can be discontinued or its dose reduced and adverse effects can be expected to disappear promptly. It is now common practice to continue beta blocker administration through the entire perioperative period in patients undergoing coronary bypass surgery,[21] because abrupt cessation has been associated with severe adverse effects.[22] However, some patients receiving beta blockers require inotropic support to be weaned off bypass and have poor hemodynamic performance in the early postoperative period. Using a continuous infusion of ASL-8052, beta blockade could be maintained until just before the thoracotomy, then discontinued during the perioperative period, and reinstituted just as soon as hemodynamic stability has returned postoperatively. The frequently observed increased postoperative sympathetic tone with resultant tachycardia and hypertension could thus be treated safely with ASL-8052.

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Sympathetic Denervation Limited to a Region of Acutely Ischemic Canine Myocardium Increases Excitability Threshold and Duration of Bipolar Electrograms

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This study determines the direct effects of sympathetic denervation on excitability threshold and bipolar electrograms in acutely ischemic myocardium. Regional denervation was performed by application of phenol to the epicardium surrounding the ischemic zone in order to eliminate the possible hemodynamic effects that global cardiac denervation may exert on the ischemic zone. Data were obtained during serial occlusions (≤6 minutes in duration) of left anterior coronary artery in open-chest dogs with sympathetic denervation performed before the last occlusion. Late diastolic threshold was measured every 5 seconds by a constant voltage pacemaker which automatically registered threshold in stimulus duration. During ischemia, regional denervation (n = 9) increased peak excitability threshold from 240 ± 51 (standard error of the mean) to 552 ± 182 μs ($p < 0.05$) and prolonged electrographic duration in epicardium from 19 ± 3 to 25 ± 4 ms ($p < 0.025$) and in endocardium from 20 ± 3 to 25 ± 4 ms ($p < 0.01$). Phenol application did not alter aortic pressure, ischemic wall motion (sonomicrometer technique), or ischemic zone blood flow (microsphere technique). Thus, acute sympathetic denervation when limited to ischemic myocardium increases the peak excitability threshold and concomitantly prolongs duration of bipolar electrograms.

Sympathetic neural input to the heart importantly affects the electrophysiologic properties of ventricular myocardium. In normal myocardium, sympathetic nerve activity influences duration of the refractory period,[1,2] but not late diastolic excitability threshold or conduction velocity.[3–7] Sympathetic neural influences may also affect electrophysiologic characteristics of ischemic myocardium since stellate ganglionectomy or stimulation may affect the tendency to ventricular fibrillation during myocardial ischemia.[8–13] Recent work has suggested that acute surgical interruption of the stellate ganglia reduced the extent of epicardial electrographic alterations produced by ischemia.[14] The present study examines the direct effects of sympathetic denervation on excitability and conduction by producing denervation limited to the ischemic zone. By this means, we can avoid the global cardiac and systemic effects of stellate ganglia interruption which may indirectly influence electrophysiologic properties of the ischemic zone.

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Methods

General: Healthy mongrel dogs weighing 14 to 25 kg were given morphine sulfate (2.3 mg/kg) intramuscularly and alpha chloralose (80 mg/kg) intravenously. We also constantly infused chloralose (16 mg/kg/h) to maintain anesthesia. The chloralose was prepared in a 2% solution dissolved in 40% polyethylene glycol (average molecular weight 200). The dogs

were mechanically ventilated. Arterial pH and partial pressures of carbon dioxide and oxygen were monitored and maintained in the normal range throughout the experiment. Sodium bicarbonate (10 mEq) was infused each hour to reverse the metabolic acidosis produced by intravenous chloralose.[15]

The sternum was split and the parietal pericardium was incised and sutured to wound edges to support the heart. The right femoral artery was cannulated with a 40 cm fluid-filled catheter which was advanced to the aortic arch and connected to a Staham P23 dB transducer to monitor pressure. To maintain normal body temperature, the animal was placed on a heating pad. In addition, the sternal incision was covered with a plastic sheet, and the operating table lamp was focused on the cardiac surface.

The left anterior descending artery was mobilized before its last large diagonal branch. In dogs with large anterior descending coronary vessels extending over the apex (carrying blood to posterior myocardium), the origins of 2 or 3 diagonal branches of the anterior descending coronary artery were dissected instead. An umbilical tape was passed beneath the vessel or vessels which were occluded with a bulldog clamp. Occlusions were 3 to 6 minutes in duration with at least 25 minutes allowed between repeat occlusions; occlusion was maintained for 6 minutes unless failure to capture or premature depolarizations prevented data collection. Duration of all the occlusions and periods between occlusions for any 1 dog were the same. Occlusions lasting <6 minutes generate reproducible changes[14] and do not produce irreversible damage.

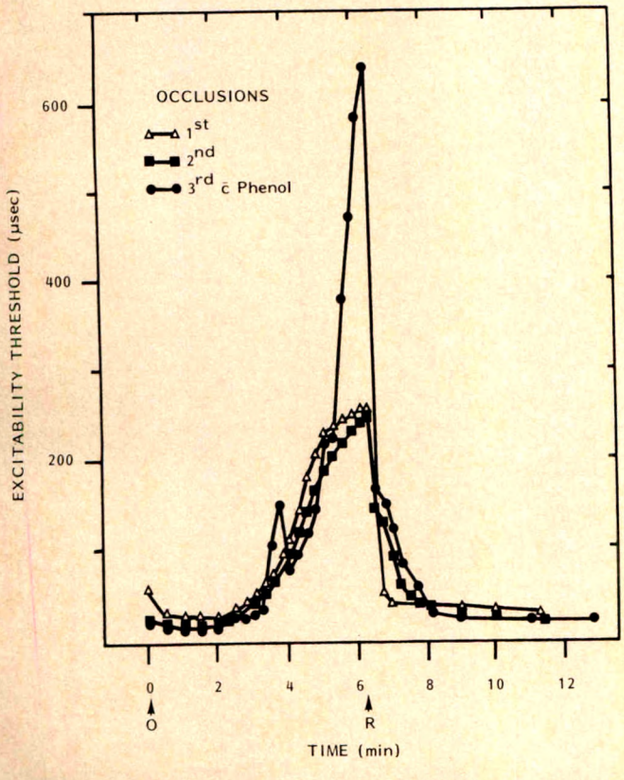

FIGURE 1. Graph showing serial excitability threshold measurements in microseconds during 3 coronary occlusions of 6.25 minutes' duration in 1 dog. Changes in excitability threshold for the first and second control occlusions are almost identical. The third occlusion after phenol encircling of the ischemic area results in a 2.5-fold increase in peak excitability threshold. 0 = occlusion; R = reperfusion.

All animals received 5,000 units of heparin before the first coronary artery occlusion.

Excitability measurement: The region of the sinus node was crushed to slow the spontaneous heart rate. The center of the left ventricular ischemic zone, identified by transient occlusion of the anterior coronary vessel(s), was paced with a unipolar cathodal stimulus at a basic cycle length of 360 to 410 ms. The cycle length was fixed in any 1 dog throughout the experiment. The anode was a 3.5 cm diameter electrode located in the subcutaneous tissue of the abdomen. The electrode delivering ventricular stimuli was either an epicardial or endocardial Teflon® coated stainless steel wire electrode (0.107 mm diameter bare only at the tip) or an acrylic plaque electrode (1 mm diameter stainless steel embedded in 1 cm diameter acrylic) sutured to the epicardial surface. Similar results occurred with both electrodes, and therefore the data were combined.

Excitability was measured by 2 methods. In the first method, stimuli were delivered to the ischemic zone electrode by an automatic threshold following pacemaker (Fig. 1).[16,17] At constant voltage (usually 2 V), the pacemaker decreased the duration of the stimulus in 2 μs steps until failure to capture occurred. The latter was determined with a separate sensing electrode; if no ventricular response was registered, the pacemaker recorded the duration of the stimulus that produced capture immediately before the subthreshold stimulus. The next stimulus duration was increased by 20 μs and was placed just 60 ms after the subthreshold stimulus; thus, the pacing cycle length stayed uniform except for 1 cycle 60 ms longer than the rest occurring at least every 5 seconds. Measurement of diastolic excitability threshold in this fashion is accurate to 1.5 μs.[17]

In the second method, constant current stimuli were delivered to the ischemic zone electrode. This method was used to exclude the possibility that changes in tissue impedance influenced the experimental results. A pacemaker set at a basic cycle length of 370 ms drove a constant current source at initially 2 times diastolic threshold. The dial regulating the current source was gradually turned to a lower intensity until ventricular capture failed, determined by visual evaluation of a cathode ray oscilloscope recording the electrographic responses of each stimulus. When failure to capture occurred, the current was read off the dial and recorded by an assistant. The dial was then turned to a higher current intensity until capture occurred. This sequence was repeated every 15 seconds.

Electrographic recording: Bipolar electrograms were monitored constantly with pairs of Teflon-coated stainless steel wires (1 to 2 mm interelectrode distance) placed in the endocardium and epicardium of the ischemic zone ≤1 cm from the pacing electrode and in the mid-wall of the posterior left ventricle. These sites were verified at the end of the experiment. The signals were amplified, filtered between 1.2 and 500 Hz, displayed on a storage oscilloscope, and recorded simultaneously on a stripchart recorder at 400 mm/s. Measurements were performed on the recordings obtained just before the delivery of the subthreshold pacing stimulus. These measurements were performed only on electrograms from recording sites which maintained the same basic contour and activation sequence (compared with other electrograms) during coronary occlusions (Fig. 2), suggesting that activation of the muscle was similar with each occlusion. Electrographic duration was measured from the first to the last definable rapid deflection from the isoelectric line (Fig. 2). Amplitude was the vertical distance between the largest positive-going wave to the largest negative-going wave of the electrogram. Measurements performed in this manner on 2 sequential electrograms did not differ.

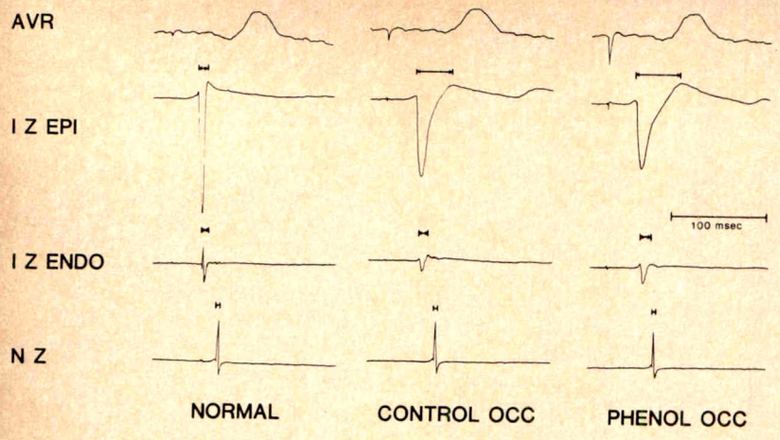

FIGURE 2. Left, "normal" indicates recordings before coronary occlusion. **Middle,** "control occlusion" indicates recordings during the sixth minute of occlusion showing a larger pacing spike in AVR (indicating a higher pacing threshold) and prolongation of electrogram duration (indicated by the distance between **vertical bars**) in ischemic zone epicardial and endocardial leads compared with the same leads before coronary occlusion and to the normal zone lead. Although not shown here, after reperfusion, all recordings return to normal. **Right,** "phenol occlusion" refers to recordings during the sixth minute of occlusion after phenol treatment. Note the still larger pacing spike and further prolongations of electrogram duration in IZ epicardial and IZ endocardial compared to control occlusion. AVR = surface electrographic lead; IZ EPI and IZ ENDO = ischemic zone epicardial and endocardial electrograms; NZ = normal zone electrogram; OCC = occlusion.

Microsphere blood flow measurements: Regional left ventricular blood flow was measured using microspheres of 7 to 10 μm diameter labeled with scandium-45, niobium-95, tin-113, ruthenium-103, and chromium-51. The spheres were suspended in dextran and vigorously agitated mechanically for 5 minutes. Blood was withdrawn from 2 large arteries at 2.06 ml/min, starting 1 minute before and continuing 3 minutes after injection. For each measurement, approximately 2×10^6 microspheres were injected over a 10-second period into a cannula placed in the left atrial appendage. Three to 4 g samples from normal zones were taken from the anterior base, posterior base, and posterior apex of the heart. These positions were chosen since they were sites in which recording electrodes were placed. Samples of similar mass from the center of the ischemic zone were taken from myocardium in which electrograms were recorded and in which pacing stimuli were administered. All samples were divided into endocardial, mid-wall, and epicardial thirds. They were weighed to the nearest milligram and placed in plastic tubes for counting in a well scintillation counter. The reference blood samples were counted similarly.

Myocardial blood flow was calculated as follows: Blood flow (in milliliters per minute × 100 g) = counts per gram of tissue × 100 × blood withdrawal rate (from reference arteries) ÷ total counts in the reference blood samples (averaged from femoral and brachial arteries). The calculations were performed for each sample with a computer. Since the endocardial, mid-wall, and epicardial blood flows changed similarly with each occlusion, the ischemic zone samples were pooled.

Sonomicrometer measurements: To evaluate the effect of sympathetic denervation on wall motion, sonomicrometer measurements of myocardial segment length in the ischemic region were studied.[18,19] A pair of 1.5 mm diameter 5 mHz piezoelectric crystals was implanted in the left ventricular myocardium in the center of the ischemic zone surrounding the pacing electrode. Analog signals were recorded simultaneously with electrograms and arterial pressure. End-diastolic segment length (EDL) was measured (in millimeters) at the onset of the endocardial electrogram (recorded from an adjacent electrode). End-systolic length (ESL) was measured at the dicrotic notch of a simultaneously recorded aortic pressure tracing.[18]

Protocols: Measurements of diastolic excitability threshold were obtained continuously. Electrogram recordings were made every minute after coronary occlusion up to 6 minutes. In preliminary experiments, it was noted that the first coronary occlusion of a series usually resulted in greater peak excitability threshold increases and greater maximal electrogram durations than subsequent coronary occlusions. Thereafter, serial occlusions were reproducible (see Group 1 data). Therefore, in this report (except for Figure 1), control data refer to the second occlusion.

Initially, animals were divided randomly into 2 groups. In the control Group I (n = 8), the third occlusion was performed without sympathetic denervation. In the phenol Group II (n = 9), 25 minutes before the third occlusion, animals underwent regional sympathetic denervation by application of a thin circle (3 cm diameter) of 88% phenol (carbolic acid) surrounding the ventricular epicardium of the area to be made ischemic. Such a procedure interrupts sympathetic innervation to the encircled epicardium and underlying endocardium.[20–22] In these groups blood flow was measured during each episode of ischemia 1 minute before release of the oc-

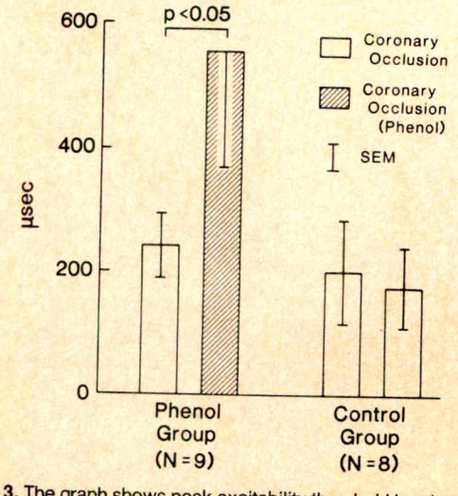

FIGURE 3. The graph shows peak excitability threshold in microseconds during sequential coronary occlusions in the phenol group (which had phenol applied to the epicardium surrounding the ischemic zone) and the control group (which had no intervention between occlusions). Note the further increase in peak excitability occurring only after the phenol application. SEM = standard error of the mean.

TABLE I Wall Motion Data (mm)

	Preocclusion	Occlusion	Intervention	Postintervention Preocclusion	Postintervention Occlusion
Group III (n = 6)					
EDL	10.9 ± 0.6	11.9 ± 0.6	None	10.9 ± 0.6	12.2 ± 0.6
ESL	10.8 ± 0.6	13.2 ± 0.7		11.0 ± 0.7	13.4 ± 0.8
Group IV (n = 9)					
EDL	9.3 ± 0.6	10.5 ± 0.6	Phenol	9.5 ± 0.8	10.6 ± 0.7
ESL	8.5 ± 0.6	11.0 ± 0.7		9.2 ± 0.8	11.2 ± 2.3

EDL = end-diastolic length of segments before and during ischemia; ESL = end-systolic length of segments before and during ischemia.

clusion and during at least one control period 25 minutes after the preceding occlusion.

To evaluate the possibility that changes in ischemic wall motion resulted from the the sympathetic interventions, we repeated the above protocols in separate experiments while recording segment length in the ischemic muscle from which electrophysiologic measurements were also recorded. Again, animals were assigned randomly to 2 groups. In Group III (n = 6), the third coronary occlusion was performed without sympathetic intervention. In Group IV (n = 9), phenol treatment was performed at least 25 minutes before occlusion 3.

Finally, a group of 3 dogs was studied employing constant-current stimulation to evaluate the possibility that changes in tissue impedance could account for the results. In 1 of these, reserpine (0.25 mg/kg) was given intraperitonally for 2 days before study to determine whether phenol application produced electrophysiologic effects separate from sympathetic denervation.

Effective refractory period testing and sympathetic nerve stimulation: To demonstrate whether phenol or ischemia alone produced regional sympathetic denervation, we measured the response of effective refractory period in various ventricular sites during electrical stimulation of sympathetic nerves at the end of each experiment as previously described.[22] After reperfusion after the final coronary artery occlusion, the central connections of both stellate ganglia were cut and prepared for stimulation. Endocardial and epicardial test sites in the anterior wall (from which electrogram changes were recorded during ischemia) and electrode sites from the posterior apex and anterior base (normal perfused zones) underwent refractory period testing. Testing was performed before and during continuous sympathetic nerve stimulation in each site.

Statistical methods: The data are expressed as mean ± standard error. Comparisons within the groups were performed by 2-way analysis of variance employing Duncan's multiple range test for comparisons.[23] Statistical significance was ascribed to p values <0.05.

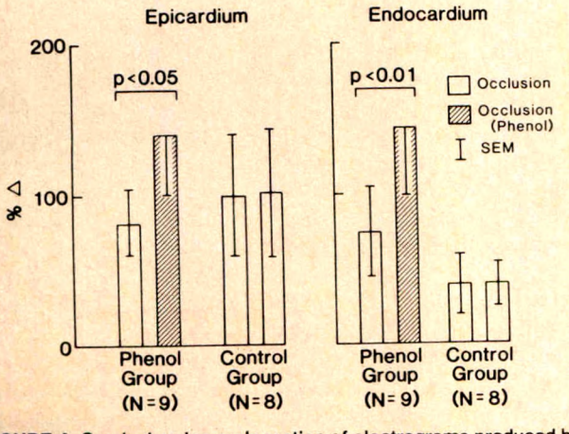

FIGURE 4. Graph showing prolongation of electrograms produced by ischemia expressed as percent change from before each occlusion in epicardium (**left**) and endocardium (**right**). The phenol group had phenol applied to the epicardium surrounding the ischemic zone between occlusion while the control group had no intervention between occlusion. Note that the electrographic duration was further prolonged by phenol in both epicardium and endocardium. SEM = standard error of the mean.

Results

Excitability data (Fig. 1 and 3): During coronary occlusion, the excitability threshold decreased in the first few minutes of occlusion and then gradually increased to a value which was maximal or peak immediately before reperfusion (Fig. 1). After reperfusion of the coronary artery, the excitability threshold returned to control levels. Peak excitability threshold significantly increased during coronary occlusion only in Group II after phenol (Fig. 3).

In 2 dogs with constant-current measurements, excitability peak threshold during ischemia increased from 44 to 200 μA and from 430 to 1200 μA after phenol application. In the animal pretreated with reserpine, there was no change in excitability threshold after phenol nor was any detectable norepinephrine found in the ventricular tissue (measured by a modification of the Anton and Sayer alumina-trihydroxyindole procedure[24]).

Electrographic data (Fig. 2 and 4): Before coronary occlusion, the electrographic duration averaged 11 ms and ranged from 7 to 15. Ischemic zone electrograms prolonged during each occlusion while normal zone electrograms did not change. The amount of prolongation in electrographic duration from the ischemic zone was progressive with each minute of coronary occlusion. However, there were no differences in electrogram duration comparing similar time after onset of coronary occlusion in Group I at all or in Group II until just before reperfusion. In the latter, there was a significant increase in electrogram duration from both ischemic epicardium (from 19 ± 3 to 25 ± 4 ms, p <0.025) and endocardium (from 20 ± 3 to 25 ± 4 ms, p <0.01) which occurred during the occlusion after phenol (Fig. 4).

Electrographic amplitude decreased with each coronary occlusion. However, no significant differences ($p > 0.25$) in electrographic amplitude were recorded in ischemic areas in either group.

Hemodynamic data (Fig. 5, Table I): In Groups I (control) and II (phenol), no significant aortic pressure differences occurred with coronary occlusion or between occlusions. In neither group were there significant differences ($p > 0.25$) in blood flow in normal (Group I, 80 ± 12 to 81 ± 5 ml/100 g/min; or Group II, 84 ± 15 to 73 ± 17 ml/100 g/min) or ischemic zones (Fig. 5) produced between occlusions. Blood flow returned toward normal levels on reperfusion.

The 2 groups reported in Table I yielded similar results in peak excitability threshold and electrogram duration as in corresponding Groups I and II. Just before reperfusion, when peak excitability threshold was highest, there were no significant differences in EDL or ESL ($p > 0.1$) when either no intervention or phenol was applied between occlusions (Groups III and IV).

Effective refractory period data: In dogs without phenol treatment, stimulation of the ansa subclavia shortened effective refractory period in 6 normal sites from 182 ± 25 to 163 ± 19 ms ($p < 0.01$) and in 8 previously ischemic sites from 198 ± 18 to 182 ± 14 ms ($p < 0.01$); the percent change in the former (9.6 ± 1.8) was not different ($p > 0.1$) from the latter (7.7 ± 1.6). By contrast, phenol-treated areas demonstrated no change in refractory period in endocardium (159 ± 7 versus 159 ± 7 ms, $p > 0.1$) or in epicardium (164 ± 6 versus 165 ± 6 ms, $p > 0.1$), while untreated sites in the anterior base (from 161 ± 11 to 150 ± 11 ms, $p < 0.01$) and in the posterior apex (from 164 ± 7 to 146 ± 6 ms, $p < 0.01$) shortened during sympathetic nerve stimulation. Thus, in these experiments phenol treatment but not serial coronary occlusion prevented refractory period responses to sympathetic nerve stimulation.

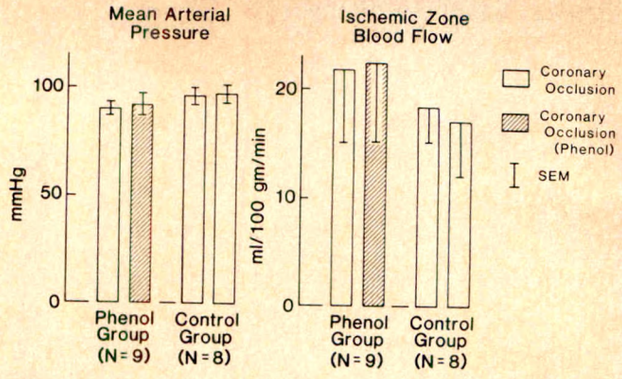

FIGURE 5. Graph showing mean arterial pressure (**left**) and absolute ischemic zone blood flow measured by radiolabeled microspheres (**right**). Sequential coronary occlusions were associated with no change in mean arterial pressures and ischemic zone blood flows in both the phenol and control groups.

Discussion

There are 2 new observations in this study. Acute sympathetic denervation when limited to ischemic myocardium increases peak excitability threshold and comcomitantly prolongs duration of electrograms in epicardium and endocardium. These electrophysiologic effects of regional denervation are not associated with changes in aortic pressure, ischemic wall motion, or ischemic zone blood flow, suggesting that they were due to the direct effects of withdrawal of sympathetic nerve influence in the ischemic zone.

Effects of regional sympathetic denervation: Previous studies have demonstrated that phenol application to the surface of the canine heart causes local denervation[20–22] by producing necrosis of epicardial sympathetic nerves which travel in the superficial 0.25 mm. The encircled tissue, being 2 to 3 cm away from the necrotizing effects of phenol, responds normally to cathecholamine[22] and after reserpine pretreatment shows no effect of phenol whatsoever. In the present study, we proved that the phenol treatment produced sympathetic denervation since it prevented refractory period responses to sympathetic nerve stimulation in the ischemic zone after reperfusion. In addition, we showed that previous transient ischemia alone does not impair refractory period responses to sympathetic nerve stimulation.

The acute application of phenol significantly increased peak excitability threshold compared with that produced by ischemia alone.[16] We considered several possibilities to explain these results. First, aortic pressure did not change with phenol denervation. Second, myocardial segment lengths in the ischemic zone were unchanged with phenol denervation. Third, ischemic zone blood flow did not change with phenol denervation. Taken together, these data suggest that the degree of ischemia present in the center of the regionally denervated zone was unchanged.

Therefore, we believe that elevation of peak excitability threshold by phenol denervation was due to withdrawal of direct effects of sympathetic neural influence on ischemic myocardium. A mechanism for this effect is suggested by previous in vitro studies. Acute ischemia produces depolarization of Purkinje fibers and ventricular muscle studied in vitro[25] and increased excitability threshold of subepicardial ventricular muscle studied in vivo.[26] Catecholamines may reduce the change in excitability threshold by minimizing the extent of cellular depolarization.[27] Our data may be an in vivo demonstration of the withdrawal of these electrophysiologic effects of sympathetic influences on depolarized and relatively inexcitable ischemic myocardial cells.

Because excitability is a major determinant of conduction velocity in Purkinje fibers,[28] we expected and found that electrographic duration increased along with peak excitability threshold when both measurements were performed in closely adjacent ischemic areas subjected to sympathetic denervation. These data appear compatible with effects of sympathetic influences on dV/dt and conduction velocity of depolarized Purkinje fibers in vitro.[29]

Our electrographic duration data appear contrary to that of Ruffy et al.[14] They showed that the epicardial electrographic duration shortened (toward normal) after stellate ganglionectomy. In other experiments not herein reported, we performed stellate ganglionectomy employing the methods of the present study. Similar to the present data, we found that stellate ganglionectomy increased excitability threshold but, in contrast, stellate ganglionectomy did not prolong ischemic zone electrograms as the regional denervation did. It is possible that phenol treatment may have affected ischemic zone blood flow differently than stellate ganglionectomy; however, data in chronically denervated animals studied by Barber et al[30] suggest that blood flow to ischemic zones is also unchanged with a global cardiac denervation. It is more likely that decreases in mean arterial pressure similar to those reported by Ruffy et al and a prolongation of ischemic zone segment length after stellate ganglionectomy could have resulted in decreased oxygen demand and a lessening of ischemic injury which may reverse the prolongation of ischemic zone electrogram.[31] Thus, we believe that the data of Ruffy et al reflect the electrophysiologic effects of both direct sympathetic influence on the ischemic zone and indirect effects of global hemodynamic changes which may decrease the degree of ischemia. Our results may be interpreted as reflecting electrophysiologic changes resulting from regional denervation alone.

Consideration of the model: In assessing the results of this study, several points should be emphasized.

First, all experimental variables were measured during constant pacing of the ischemic area since continuous excitability threshold was evaluated. Dyssynergy was therefore produced,[32] which may have influenced the results. For example, regional sympathetic denervation with phenol may not have produced further ischemic segment lengthening because of this dyssynergy. In addition, it is possible that phenol, by decreasing sympathetic influences to the ischemic tissue, might decrease the size of the ischemic zone. Our data do not allow us to judge the effect of phenol on ischemic zone size; however, the fact that blood flow to and wall motion of the tissue where electrical testing was performed did not change suggests that hemodynamic factors were an unlikely explanation for the electrophysiologic results.

Second, the present studies were performed in anesthetized open-chest dogs, which are likely to be under high baseline sympathetic influence. However, increased sympathetic influences are commonly found in patients with arrhythmias in acute myocardial infarction.[33] Therefore, the present observation may be relevant to the properties of ischemic myocardium responsible for arrhythmias.

A final limitation of the present study concerns the fact that only short-term occlusion of ≤6 minutes in duration were studied. It is possible that different results might pertain at a later time in the course of acute coronary occlusion. However, this early period after occlusion is a time at which a greater propensity to the development of spontaneous ventricular arrhythmias occurs[34]; therefore, our attention to this time frame may be important.

Possible significance for development of arrhythmias: Previous studies have suggested that *acute* interruption of sympathetic neural influence prevents ventricular fibrillation in dogs undergoing coronary artery occlusion.[8,9,11] These results have been challenged by Ebert et al,[10] who maintained that chronic denervation with depletion of catecholamine stores is necessary to produce protection from arrhythmias. The results of the present study and that of Ruffy et al[14] suggest electrophysiologic mechanisms which could prevent ventricular fibrillation, since acute sympathetic denervation can influence excitability and conduction in ischemic myocardium during the first 6 minutes of coronary occlusion. We speculate that sympathetic denervation might further increase excitability threshold or render certain areas inexcitable in the ischemic zone and thus eliminate potential pathways for arrhythmogenesis. Other mechanisms produced by the multiple effects of stellate ganglionectomy, such as decreased dispersion of refractoriness[35] or decreased degree of ischemia, may also be operative.

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Transvenous Ablation of the Atrioventricular Conduction System in Dogs: Electrophysiologic and Histologic Observations

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The correlation of histologic and electrophysiologic findings in dogs undergoing transvenous ablation of atrioventricular (AV) conduction has not been described. The creation of complete AV block in 10 dogs was attempted by delivering a direct-current shock transvenously through a standard tripolar electrode catheter. The catheter was positioned to record the largest unipolar atrial and His bundle electrograms. A 280 J shock was delivered to the recording electrode by a standard cardioversion unit. After 1 shock, all dogs were in complete AV block refractory to isoproterenol (1 to 4 μg/min) and atropine (0.5 to 2.0 mg). Four weeks later, 5 dogs remained in complete AV block, 1 had first-degree block, and 4 had resumed normal AV conduction. Each dog with complete heart block had histologic evidence of severe damage to the AV node, His bundle, or both. On gross examination, these dogs were found to have discrete scars at the base of the septal leaflet of the tricuspid valve. Of the 5 dogs that had resumption of AV conduction, only 1 had histologic evidence of significant damage to the AV conduction system. That animal manifested a marked increase in the P-R interval (100 to 210 ms). Although temporary heart block occurred in each animal, chronic interruption of AV conduction was more difficult. Catheter location, atrial and His bundle electrogram relations, and the electrode used for delivery of energy were factors determining the effectiveness of this technique.

Intentional interruption of normal atrioventricular (AV) conduction by destruction of the AV node is possible with a variety of techniques in the animal laboratory.[1–9] Similarly, there are several methods for therapeutic ablation of the AV conduction system in patients with medically refractory supraventricular tachycardias.[10–22] Until recently, methods for interruption of AV conduction in man and in laboratory animals have required an open-chest procedure. Several current studies suggest that closed-chest ablation of atrioventricular conduction is feasible and effective with a variety of techniques.[23–31] One method of particular interest is that performed by delivery of a direct-current shock through a standard His bundle catheter.[30] The equipment required is that found in any laboratory capable of recording His bundle electrograms and providing direct-current cardioversion. The effective technique can be readily mastered and avoids the risks attendant to thoracotomy. Although this technique is easily applied and appears relatively safe, the degree of tissue destruction resulting from this method is unknown. This study was therefore undertaken to correlate the electrophysiologic consequences of such a direct-current shock with histologic changes in the AV conduction system.

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Methods

Ten dogs weighing 15 to 20 kg were studied. After induction of anesthesia with 30 mg/kg of pentobarbitol, each dog was intubated and ventilated. Using sterile technique, a standard 6 Fr tripolar intracardiac recording catheter (United States Catheter Instrument) with 1 cm interelectrode distances was inserted through the femoral vein and positioned in the region

of the His bundle. Two unipolar electrograms (1 from the distal pole and 1 from the middle pole) were filtered to pass 5 to 1,000 Hz and were displayed by way of a switch box (Fig. 1) on a Hewlett-Packard oscilloscope and chart recorder. A bipolar signal, recorded from the distal and middle poles of the catheter, was filtered to pass 50 to 1,000 Hz and was displayed with the unipolar signals. The proximal pole was not utilized. A back paddle was positioned between the spine and left scapula and was connected to the anodal output (sink) of the cardioversion unit. The switch box (Fig. 1) allowed the catheter electrodes to be utilized first for recording purposes, and subsequently, as a vehicle for current delivery. When the electrode showing the largest unipolar His deflection was identified, the defibrillator was charged. With a large, stable, unipolar His deflection still evident, the defibrillator was discharged synchronously with the QRS complex by way of the switch box through the electrode recording the largest His electrogram. Each dog received a single direct-current shock (280 J delivered, not stored) resulting in complete heart block. After induction of complete heart block, atropine (0.5 to 2.0 mg) and isoproterenol (1 to 4 μg/min) were used in an attempt to improve atrioventricular conduction. When heart block proved refractory to pharmacologic manipulation, the animals were allowed to recover from anesthesia.

All dogs were monitored for a 2-hour interval immediately after the shock. This was repeated 1 week and 4 weeks later to observe the occurrence of spontaneous arrhythmias. After 4 weeks, intracardiac recordings were obtained (Fig. 2) in addition to surface electrograms. During each observation period any sign of tricuspid insufficiency was looked for (for example, holosystolic murmur, neck vein distention, or ascites). Four weeks after shock, the animals were killed for gross and microscopic examination. Each heart was examined for a flail or torn tricuspid leaflet, right atrial dilatation, or right ventricular dilatation—findings consistent with tricuspid insufficiency. (Three representative gross specimens are illustrated in Figure 3.) After visual inspection for structural damage, the entire section of the AV node and His bundle were embedded as 1 block. This included the lower atrial septum and the upper ventricular septum. The block was sectioned serially, perpendicular to the interventricular septum, and slides were made at each millimeter. An average of 25 sections was obtained from each dog. Each section was stained with hematoxylin and eosin and was studied for damage to the AV conduction system and adjacent myocardium. A von Kossa stain was used to identify microscopic calcium deposits. The amount of damage to the approaches to the AV node, the AV node proper, the penetrating portion of the bundle of His, the branching portion of the bundle of His, and the proximal right bundle branch was determined from the histologic sections. The amount of destruction of each of these regions was estimated from the amount of tissue necrosis and from the amount of connective tissue deposited.

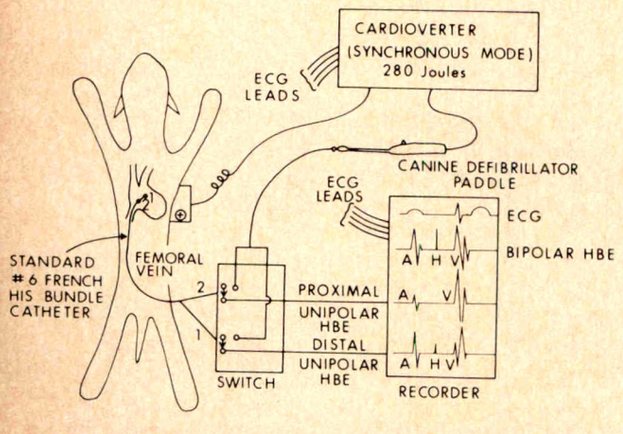

FIGURE 1. Schema for transvenous ablation of the atrioventricular conduction system using a standard cardioversion unit and recording catheter. After a large, stable His bundle deflection is identified, a direct-current discharge (280 J) is delivered by way of a switch box to the recording electrode. A back paddle serves as a sink, completing the circuit. ECG = electrocardiogram; HBE = His bundle electrogram.

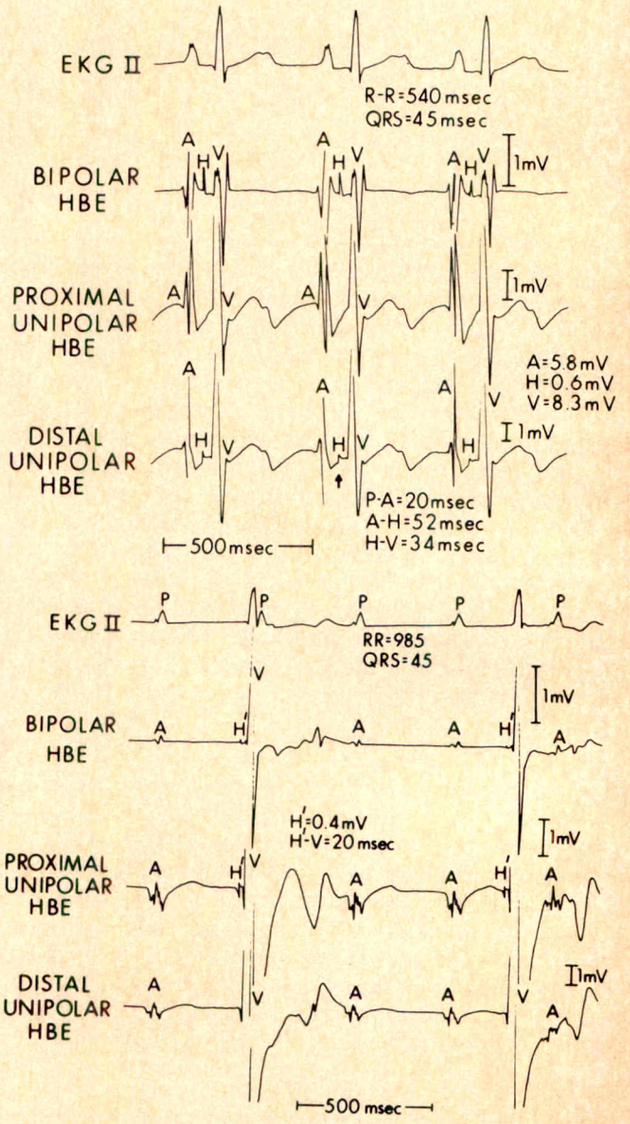

FIGURE 2. Intracardiac recordings immediately before (**top**) and 4 weeks after (**bottom**) atrioventricular interruption. These electrograms were obtained from the same animal whose gross specimen is shown in Figure 3A. The **top panel** demonstrates sinus rhythm with the His deflection (H) identified on the bipolar and distal unipolar electrograms. Four weeks after the shock, complete heart block is evident in the **bottom panel.** The earliest recorded deflection from specialized conduction tissue (H′) is now of smaller amplitude (0.3 mV) than the His deflection seen before ablation (0.5 mV). This suggests the ventricular escape rhythm arises in the distal segment of the His bundle or proximal right bundle branch. Note that the QRS morphology is unchanged after the shock. ECG = electrocardiogram; HBE = His bundle electrogram.

Damage was estimated using a scale of 0 to 3+ with 0 corresponding to no damage, 1+ representing destruction of less than one third of the structure, 2+ representing destruction of one third to two thirds of the structure, and 3+ representing destruction of more than two thirds of the structure (Tables I and II). The volume of damaged ventricular myocardium was estimated by projecting serial histologic sections onto a display screen from a modified slide projector and then planimetering the area of damaged ventricular myocardium for each section.

Results

Immediately after a single direct-current 280 J shock, all 10 dogs had complete heart block refractory to isoproterenol and atropine. Recovery from the procedure was without incident. Upon initial follow-up evaluation 1 week after shock, only 5 dogs remained in complete heart block while 5 resumed conduction through the AV node-His bundle. Those 5 dogs that were in complete heart block 1 week after the shock remained so for the 4-week observation period. No dog had spontaneous arrhythmias, sudden death, or signs of hemodynamic compromise.

Of the dogs with complete heart block 4 weeks after the shock, 4 had an escape rhythm QRS duration that was unchanged from the preshock QRS duration (Table III). Only 1 dog had a prolonged QRS duration after shock (from 43 to 65 ms). This was because of damage to the right bundle branch. Before heart block, the interval from the His bundle deflection to the onset of ventricular depolarization (H-V) ranged from 28 to 44 ms in the 5 dogs. After shock, the interval from the onset of the earliest recorded deflection from specialized conduction tissue to the onset of ventricular depolarization (H′-V) was less than the respective preshock H-V in all dogs in which H′ could be found (Table III). No His deflections were observed to follow the atrial electrogram.

Histologic examination of the dogs with chronic complete heart block demonstrated that each dog had severe damage to the approach to the AV node, to the

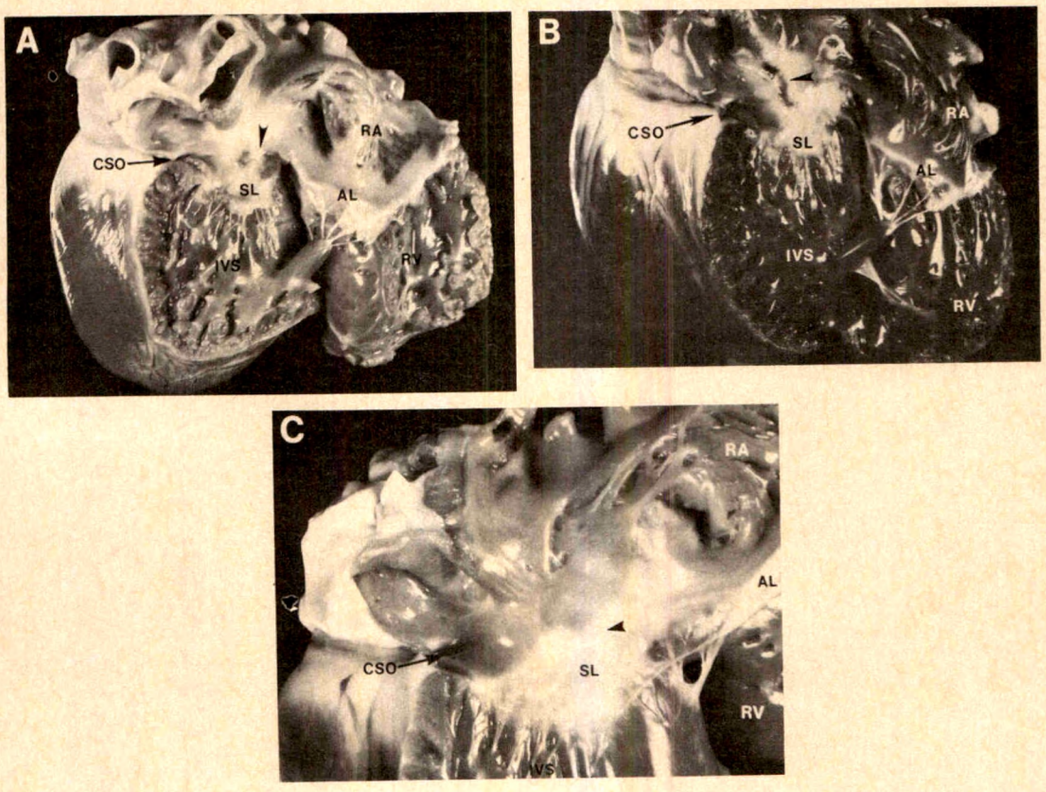

FIGURE 3. Gross specimens demonstrating location and character of injury in 3 dogs. In all 3 specimens the anterior free wall of the right ventricle (RV) has been dissected back to expose the interventricular septum (IVS) and the septal leaflet of the tricuspid valve (SL). The coronary sinus orifice (CSO) is a slitlike structure in these views. The anterior leaflet (AL) of the tricuspid valve is on the inner surface of the free right ventricular wall which is partially dissected back. The **arrowhead** designates the injured tissue. Note the absence of septal perforation or flail tricuspid leaflets in all 3 hearts. **A,** the effect of the shock resulting in the largest amount of injury to the tricuspid valve. This shock was delivered to the middle pole of the His bundle catheter and is just "distal" to the ideal location, which would be centered at the base of the septal leaflet of the tricuspid valve. This shock involved more of the interventricular septum than did shocks delivered through more proximally situated catheters and therefore resulted in right bundle branch block. In addition, the base of the septal leaflet of the tricuspid valve is fibrosed and partially adherent to the interventricular septum. Clinical tricuspid insufficiency was not observed however. **B,** demonstration of a lesion delivered through the distal catheter electrode just superior to the base of the septal leaflet of the tricuspid valve. This was the largest lesion seen after direct-current shock with the majority of injury confined to atrial tissue. Little ventricular tissue was involved. This shock damaged only the proximal atrioventricular conduction system resulting in a narrow escape rhythm. **C,** a well-placed shock delivered through the distal electrode. This lesion is less well seen grossly than the other 2, but in general is more characteristic. The pale white scar in this specimen is not well differentiated from normal tissue. Nevertheless, this adequately destroyed the approaches to the AV node, the AV node, and proximal penetrating bundle resulting in a narrow escape rhythm. This lesion actually resulted in the greatest amount of ventricular damage. The histologic findings from this specimen are shown in Figure 4.

TABLE I Heart Rhythm and Histologic Findings 4 Weeks After Direct-Current Shock

Dog	Rhythm	Tissue Injury (0 to 3+)				
		AV Node Approach	AV Node	Penetrating His	Branching His	Right Bundle
1	CHB	...	...	3+	1+	...
2	CHB	3+	3+	...	...	...
3	CHB	3+	2+	...	...	...
4	CHB	3+	3+	2+	3+	3+
5	CHB	...	...	...	3+	2+
6	Sinus	...	...	...	1+	...
7	Sinus	...	...	...	...	...
8	Sinus	...	...	...	1+	3+
9	Sinus, 1° AV block	3+	3+	1+	1+	3+
10	Sinus	...	...	...	...	...

CHB = complete heart block.

TABLE II Electrocardiographic Changes Before and After Shock in Dogs With Resumption of AV Conduction

Dog	QRS Duration (ms)		P-R Interval (ms)		Damage to AV Conduction System (0–3+)
	Before	After	Before	After	
1	41	40	107	135	1+
2	47	47	82	155	0
3	41	75 (RBBB)	100	130	1+
4	48	79 (RBBB)	100	210	3+
5	60	62	72	73	0

AV = atrioventricular; RBBB = right bundle branch block.

TABLE III Correlation of Conduction System Damage With Changes in the QRS Duration and H-V Interval in Dogs With Chronic Complete Heart Block

Dog	QRS Duration (ms)		H-V Before (ms)	H′-V After (ms)	Regions With Severe Damage to AV Conduction System
	Before	After			
1	45	45	34	20	Penetrating His bundle
2	46	48	44	39	AV node approach and AV node
3	46	42	31	26	AV node approach
4	43	65 (RBBB)	30	18	AV node approach, AV node, branching His bundle and RBB
5	42	44	28	...	Branching His bundle

AV = atrioventricular; H-V = His-ventricular interval; H′-V = earliest specialized conduction tissue-ventricular interval; RBB = right bundle branch; RBBB = right bundle branch block.

AV node, to the penetrating His bundle, to the branching His bundle or to some combination of these (Table I). One dog with QRS prolongation and right bundle branch block after shock (dog 4, Tables I and III) had severe damage to the proximal right bundle branch as well as to the AV node and His bundle. In all dogs with complete heart block, areas of injury were characterized by dense, fibrous tissue. In some injured areas, calcium deposits were surrounded by granulomatous inflammation with giant cell formation. One dog (dog 2, Tables I and III) had vasculitis of the AV nodal artery in addition to conduction tissue injury.

Although each dog with chronic complete heart block had severe damage to some segment of the AV conduction tissue, none had perforation of the interatrial or interventricular septum. In addition, there was no thinning of the interventricular septum. All of the dogs with chronic complete heart block had a mild fibrous reaction at the base of the septal tricuspid leaflet at the point where it originates in the lower atrium at the tricuspid anulus. One dog (Fig. 3C) had an inflammatory reaction between the basal portion of the tricuspid septal leaflet and the septal right ventricular endocardium. Histologic evaluation of the AV conduction system from this dog is illustrated in Figure 4. Sections through the upper AV node, lower AV node, and penetrating portion of the His bundle are shown. This particular animal had the largest degree of ventricular damage despite a rather unimpressive appearance on gross examination.

When the mass of damaged ventricular myocardium was estimated by planimetry of serial sections, no dog proved to have ventricular tissue loss exceeding 65 mm^3 or 0.068 g. This compared favorably with ventricular

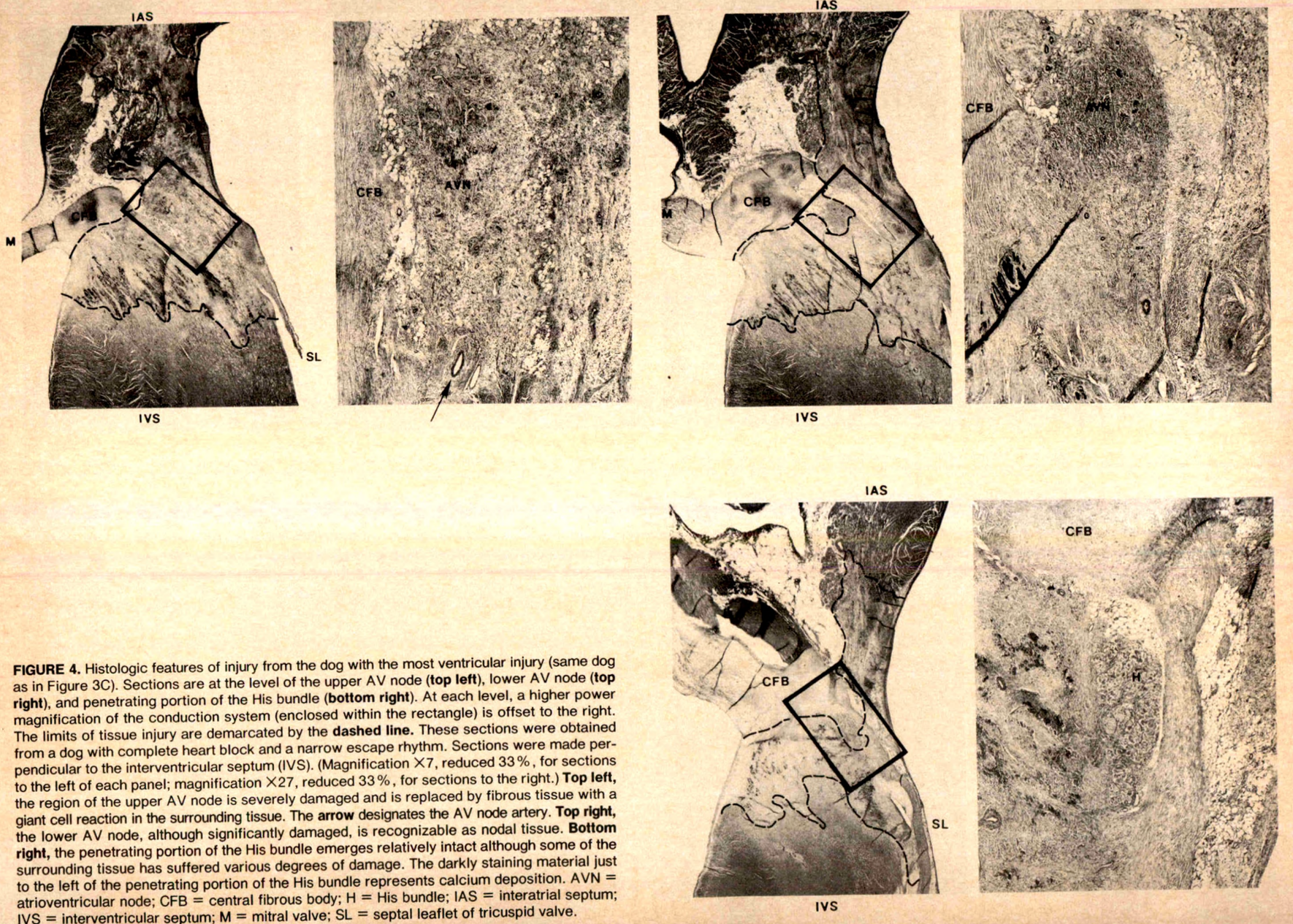

FIGURE 4. Histologic features of injury from the dog with the most ventricular injury (same dog as in Figure 3C). Sections are at the level of the upper AV node (**top left**), lower AV node (**top right**), and penetrating portion of the His bundle (**bottom right**). At each level, a higher power magnification of the conduction system (enclosed within the rectangle) is offset to the right. The limits of tissue injury are demarcated by the **dashed line.** These sections were obtained from a dog with complete heart block and a narrow escape rhythm. Sections were made perpendicular to the interventricular septum (IVS). (Magnification ×7, reduced 33%, for sections to the left of each panel; magnification ×27, reduced 33%, for sections to the right.) **Top left,** the region of the upper AV node is severely damaged and is replaced by fibrous tissue with a giant cell reaction in the surrounding tissue. The **arrow** designates the AV node artery. **Top right,** the lower AV node, although significantly damaged, is recognizable as nodal tissue. **Bottom right,** the penetrating portion of the His bundle emerges relatively intact although some of the surrounding tissue has suffered various degrees of damage. The darkly staining material just to the left of the penetrating portion of the His bundle represents calcium deposition. AVN = atrioventricular node; CFB = central fibrous body; H = His bundle; IAS = interatrial septum; IVS = interventricular septum; M = mitral valve; SL = septal leaflet of tricuspid valve.

tissue damaged by cryoablation of the AV conduction tissue, which can be greater than 2,000 mm^3 or 2.1 g for a lesion with a 25 mm diameter on the ventricular endocardial surface extending 6 mm into the myocardium.[32,33]

Five dogs that initially had complete heart block resumed AV conduction, probably after resolution of edema. Return of AV conduction in these 5 animals occurred sometime before the first postshock electrocardiogram (1 week later). In these 5 animals, AV conduction remained intact through the fourth week of observation. Gross and histologic examination revealed that only 1 of these dogs had evidence of significant damage to the approaches to the AV node, to the AV node, to the penetrating His bundle, or to the branching His bundle. The dog that did have severe damage to the approaches to the AV node and to the AV node (dog 4, Table II) had marked prolongation of the P-R interval (from 100 to 210 ms) as well as the A-H (from 66 to 130 ms) and the H-V (from 34 to 53 ms) intervals. In addition, this dog had prolongation of the QRS duration from 48 ms before shock to 79 ms after shock, with the QRS demonstrating right bundle branch block morphology as a result of severe damage to the proximal right bundle branch. Of the remaining 4 dogs that resumed AV conduction, 1 had mild damage to the branching His (dog 1, Table II), 1 had mild damage to the branching His and severe damage to the right bundle branch (dog 3, Table II), and 2 had no histologic evidence of injury to the AV conduction system whatsoever (dogs 2 and 5, Table II). Even though these 4 dogs had minimal damage to the AV conduction system, only 1 (dog 5, Table II) had no change in the P-R interval after compared with before shock. This dog was 1 of 2 that had no evidence of conduction system damage on histologic examination. The other dog (dog 2, Table II) did have prolongation of the P-R interval from 82 ms before shock to 155 ms after shock. One dog (dog 3, Table II) had right bundle branch block as a result of a shock applied too distal to the AV conduction system, injuring the right bundle branch with only mild damage to the His bundle.

Six animals received the shock through the distal electrode and 4 had the shock delivered through the middle electrode. Severe damage to the approach to the AV node, penetrating His bundle, or branching His bundle occurred with shocks delivered through the distal electrode in 5 dogs and through the proximal electrode in 1. The ratio of the atrial electrogram amplitude to the His deflection amplitude for those dogs incurring severe AV conduction system injury ranged from 4 to 10 (mean 7.6 ± 2.0). The ratio of the atrial electrogram amplitude to the His deflection amplitude in those dogs without severe conduction system injury was <4 or >10 in all but 1 animal.

Discussion

Interruption of AV conduction for refractory supraventricular tachycardia has been performed with a variety of methods.[10–22] Of these methods, cryoablation has probably offered the best control over damage to the AV node.[9,21,22] It is effective and preserves collagen fibers while leaving a well-circumscribed fibrous lesion.[9,21,22,32,33] Unfortunately, a median sternotomy is necessary for its application.

Closed-chest induction of complete heart block, on the other hand, has the obvious advantage over cryoablation and several other methods used for interruption of AV conduction because thoracotomy is not necessary. Percutaneous transvenous ablation of AV conduction as described in this report is applicable with relative ease, using a standard cardioversion unit and a standard intracardiac recording catheter. Other methods have been described for closed-chest interruption of AV conduction. These have required specially designed instruments and may yield less than optimal results. The closed-chest technique for ablation of AV conduction proposed by Beazell[26,27] involves electrocautery through a sheathed transseptal needle positioned fluoroscopically in the interatrial septum in the region of the AV node. Although successful in the short-term preparation, effective long-term interruption of AV conduction was not shown. Furthermore, 3 dogs had massive hemorrhage, perforation of the heart, or both. Gonzalez et al[29] have reported another technique requiring a specially modified quadripolar catheter. In their study, 5 of 10 dogs had complete heart block with a single 35 J shock. Four others received as many as 4 shocks to create complete heart block. In 1 dog, ventricular fibrillation developed during the shock. This method generated broad QRS complexes after shock in all animals studied, possibly reflecting characteristics of the catheter or the technique. The inability to localize a His deflection after shock may indicate a distally applied shock. Nevertheless, the escape rhythms in these animals were apparently satisfactory. Detailed histologic studies to determine whether broad QRS escape rhythms were a result of large tissue damage or of distally applied shocks were not described. These results were similar in patients who had larger energies (500 J) delivered with the same technique.[31]

Our work as well as others' suggest that the location and extent of tissue damage with the transvenous technique is probably very protocol-dependent and may prove to be more sensitively related to 1 factor over another. The findings in this study suggest that the success of our technique is dependent upon several factors. Of prime importance is catheter position. If the catheter is distal to the His bundle, right bundle branch damage is possible. Furthermore, heart block from a lesion created in a relatively distal segment of the His-Purkinje system may have a poor escape rhythm. On the other hand, a too proximal discharge may miss the AV conduction system altogether. Therefore, in addition to fluoroscopic guidance, one can properly position the catheter by observing the electrogram characteristics. Specifically, locating a relatively large atrial deflection with respect to the His deflection indicates good catheter position. In dogs, an atrial deflection-to-His deflection ratio of 4 to 10 appears to be a useful guide for proper catheter positioning over the proximal AV conduction system. A second consideration for effective energy delivery is catheter contact with the endocardial surface. The topography of the endocardial surface

overlying the AV node and His bundle is such that a catheter can firmly contact the endocardium of this region only over a small area. Considering the anatomy, the distal electrode of the catheter is more likely to securely contact the endocardium than a more proximal electrode would be. In those dogs with no damage or minimal damage to the AV conduction system, catheter contact with the endocardium may have been less than optimal, allowing much of the delivered energy to be dissipated in the blood. This may explain, in part, the greater effectiveness of using the distal electrode than the proximal one. Another factor that may be pertinent to tissue damage is current density or current flux. Current flow from the cylindrical, middle electrode with both ends adjacent to insulation differs from current passing from the cylindrical, distal electrode with a rounded free end.[34] Under similar conditions, current flux is higher from the rounded free end of a distal electrode. This theoretical consideration may further explain why shocks from distal electrodes tended to be more effective. Finally, another factor possibly related to effective ablation of the AV conduction system is the characteristic of the direct-current pulse. Since these experiments began, variability has been shown to occur in current flow, voltage, and resistance over the time during which the shock is delivered. These are dependent upon circuit characteristics and energy delivered as well as characteristics of the electrode-tissue interface. With further study, particulars of the direct-current pulse may prove important for effective ablation of AV conduction.

The anatomic findings in dogs with chronic complete heart block after application of direct-current shock suggest that tissue destruction is not extensive. The lack of atrial or ventricular septal perforation reflects the smallness of the injury (Fig. 3 and 4). Typical cardiac mass for a 20 kg dog is approximately 200 g. The fact that no dog had a ventricular volume of injury >65 mm^3 or a mass >0.068 g (<1% of myocardial mass) emphasizes how little ventricular tissue was affected. Qualitative changes, however, were significant and resembled those observed during transthoracic and directly applied paddle countershock.[35,36] Dahl et al,[35] in an experiment designed to evaluate optimal paddle size and time intervals between transthoracic discharges, found that transthoracic direct-current countershock could result in necrosis of myocardial fibers. Furthermore, in nonnecrotic myocardial fibers that retained cross striations, calcium deposition was frequent and was shown by electron microscopy to be deposited in the mitochondria. A mononuclear cell reaction was also present. Similar findings were observed by Doherty et al[36] who studied the effects of direct-current countershock delivered by paddle electrodes applied directly to the heart. Their study demonstrated increased technetium 99m-pyrophosphate uptake with repetitive shocks administered at short-time intervals compared with the same shocks delivered over longer periods. These findings were presumably a consequence of cumulative thermogenic injury, because tissue injury could be minimized by increasing the time between shocks. The cellular damage consisted of granulation of cytoplasm, nuclear pyknosis, and myocyte contraction bands. Tissue damage extended into the deeper layers with higher energy levels and with similar electrode size. The greater the shock, the more likely the tissue would develop gross patches of calcification. As demonstrated by Dahl, Doherty, and ourselves, the principle histologic changes produced by direct-current shocks are myocyte degeneration, calcium deposition, and mononuclear infiltrates. The additional finding of giant cell formation in our study probably reflects a late tissue response to calcium deposits.

The use of transvenous direct-current shock through a standard intracardiac recording catheter proved to be a safe technique for closed-chest interruption of the AV conduction tissue. Complete heart block could be consistently induced with a single shock in the acute preparation and with moderate success in the chronic situation. Successful transvenous ablation of the AV conduction system appeared to be facilitated by proximal catheter position, as judged by the relation of the atrial and His electrograms, and by use of the distal electrode. Alterations in cardiac conduction appeared to be a direct consequence of the location and degree of injury produced by the shock. Even with the largest lesion created by this technique, a small fraction of ventricular myocardium was destroyed with minimal damage to the base of the tricuspid septal leaflet and with no evidence of cardiac perforation. Several other factors attested to the technique's safety. No dog had arrhythmia during any of the postshock observation periods and no dog had sudden cardiac death. Furthermore, the integrity of the tricuspid valve remained intact as witnessed by the absence of clinical findings of tricuspid regurgitation and by the absence of an enlarged right heart at postmortem examination. This technique, therefore, promises to facilitate safe, effective induction of AV block experimentally and clinically.

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Premature Ventricular Contraction Or Ventricular Extrasystole?

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Electrocardiology is an exact scientific discipline. Yet it is, on occasion, punctuated with terms that are vague and nondefinitive. One such term is *premature ventricular contraction*, which is a nonspecific degeneration from the original term *ventricular extrasystole.* A scientific term or definition should ideally be sufficiently precise so as to be applicable to 1 circumstance only. *Premature ventricular contraction*, however, is nonspecific. The only meaning conveyed is: a ventricular contraction that is premature. Nothing else is embodied in the term. Premature ventricular beat and premature ventricular depolarization are equally vague. There are indeed many mechanisms that result in premature ventricular contractions or beats, and to which the term could be readily applied.

All of the following result in premature ventricular contractions: (1) a ventricular extrasystole (see later); (2) a manifest ventricular parasystolic discharge; (3) a ventricular capture beat; (4) a reciprocal beat of ventricular or atrioventricular junctional origin; (5) a conducted atrial or atrioventricular junctional extrasystole; and (6) a relatively early beat during atrial fibrillation. In this context, Scherf (1953)[1] specifically comments: "As far as extrasystoles in auricular fibrillation are concerned the term 'premature beats' would be altogether unacceptable."

The question may also be posed as to whether a primary electrical event should be described by the hemodynamic term *contraction* which, when it occurs, is the secondary result of the primary electrical event. Furthermore, concealed ventricular extrasystoles have been described which do not give rise to contractions at all.[2,3] It would be patently absurd to refer to these as concealed premature ventricular contractions. Confusion becomes more confounded by the term *premature junctional contraction.*[4] If *premature ventricular contraction* refers to a ventricular contraction resulting from an impulse arising in the ventricles, and *premature atrial contraction* refers to an atrial contraction resulting from an impulse arising in the atria, does a *premature junctional contraction* refer to a junctional contraction resulting from an impulse arising in the junction? Does the atrioventricular junction itself contract, and in isolation? Would a concealed atrioventricular junctional extrasystole[5,6] (due to concomitant retrograde and anterograde atrioventricular block) which does not result in a contraction anywhere in the heart still be referred to as a *premature junctional contraction?*

The term *extrasystole* was first used by Engelmann in 1896,[7] in his studies of artificial electrical stimuli applied to the heart. The use of this term was continued by other authorities of the day: Pan (1903),[8] MacKenzie (1907),[9] Rihl (1912),[10] Wenckebach (1914),[11] and Lewis (1920).[12] Very early on, the extrasystole came to be associated with a very specific property, namely, a fixed coupling of the premature beat to the preceding (usually) sinus beat: a property, moreover, that is not possessed by any of the other causes of premature ventricular contraction.

Thus, Lewis (1920),[12] for example, states: ". . . isolated extrasystoles and the first beat of a paroxysm *have the same degree of prematurity"* (italics mine). And Scherf and Schott (1953)[1] clearly state that the extrasystole is ". . . accurately coupled to the preceding beat." This is the essential feature of the ventricular extrasystole,[11–14] which should, in the context of modern electrocardiography, be defined as an impulse that arises prematurely in an ectopic ventricular focus and is fixedly coupled to the preceding beat. The term *impulse* is used for the extrasystole, not *beat* or *contraction*, because it is primarily an electrical event; *beat* is justified in the context of *preceding beat* because a complete ventricular activation resulting in a beat is necessary to precipitate or force the ensuing extrasystole. Such a definition is specific and could only be applied to a ventricular extrasystole; it excludes all other causes of premature ventricular contraction.

In this context, the Criteria Committee of the New York Heart Association[4] applies the term *premature ventricular contractions* not only to beats with fixed coupling, but also to beats with variable coupling, namely, parasystolic beats. This interchangeable application to different electrocardiographic mechanisms further emphasizes how ambiguous and vague the term really is.

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Nevertheless, the *systole* part of *extrasystole* could also be semantically challenged, because it derives from the Greek meaning "to draw together": in other words, a contraction. Yet, the term has increasingly come to have an electrical connotation. Butterworth's Medical Dictionary (1978),[15] for example, refers to *electrical systole:* "The period during which there is electrical activity relating to the stimulation and recovery of the myocardium." The concept of *electrical systole* is also becoming embodied in modern texts of electrocardiology.[16,17]

The prefix *extra* of the *extrasystole* has long been a source of unnecessary confusion. It was, for example, defined by Katz and Pick (1956)[18] as an additional beat, and hence would only apply to an interpolated ventricular extrasystole. This was neither justified by the preceding use of the word, nor supported by the succeeding voluminous electrocardiographic literature. The prefix *extra* in the context of extrasystole does not mean addition, but rather outside the normal, as in extracurricular or extraordinary.

Thus, historically, and by long-established application to a specific electrocardiographic mechanism, *ventricular extrasystole* has come to have 3 well-defined properties: (1) ectopic ventricular origin of an electrical impulse; (2) prematurity of the electrical impulse; and (3) fixed coupling of this electrical impulse to the preceding event.

The term *ventricular extrasystole* thus defines a primary electrical event, and, although open to semantic challenge (the purist would have to coin an entirely new word), is far more satisfactory than *premature ventricular contraction*, which is nonspecific, reflects a secondary hemodynamic event, and may result from several different mechanisms. Linguistically, *premature ventricular contraction* is more cumbersome, and its use, therefore, cannot even be justified or condoned on the basis of facility or economy of language. Thus, it does not simplify, it does not clarify, and it confuses.

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Identity and the Electrocardiogram, With A Note on Twins and Altered Identities

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The reproducibility, or identical characteristics, of the 12-lead electrocardiogram (ECG) in any 1 individual is so well-known a feature of electrocardiography that the clinical electrocardiographer seldom verbalizes or emphasizes this point. Indeed, it is accepted as routine that an electrocardiographic reader clearly appraises the identity of the tracings in a series of ECGs and determines that they are all from the same person. When an error of identification is made, that is, a record carries the wrong name, and appears in a series of ECGs, it is usual for the electrocardiographer to pick up this error. The record's origin is checked by comparison with previous tracings which all have more or less the same characteristics. Substitution of another's ECG for one's own is a well known attempted ploy when falsification of preinsurance information is perpetrated. This fraudulent situation can also be recognized if previous or repeated and current ECGs are available to the insurance examiner.

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There is a long and reliable clinical experience on the uniqueness of each person's ECG. The identity of one's ECG is relatively well preserved through life, and some stable features persist even when cardiac disease or drug effects alter certain parts of the tracing. The most stable features include the form and duration of the P wave (during sinus rhythm) and the duration and notching of the QRS. These waves result from depolarization of atrial and ventricular myocardium. The reproducibility or stability of these waves was very satisfactory, with only a ±15- to 30-ms variation in durations and identical numbers and locations of notchings as measured by computerized analysis of 2 to 6 records for the same normal adults. This study was part of an evaluation of a computer analysis comparison program written by myself and my colleagues.[1] In this same study the frontal plane axis of the P and QRS complexes was also constant, with a variation that seldom exceeded ±10° to 15° unless body shape or diaphragm level altered markedly.[1] S-T and T waves are less stable, being susceptible to many extracardiac influences. The P-R and Q-T intervals are relatively stable, but the P-R varies with heart rate, vagal tone, and drug effects and the Q-T with heart rate and drug effect.

When one considers the reliance placed on exactly matching electrocardiographic records arising from each individual in clinical electrocardiography, 2 related concepts are of interest: the ECG of twins and the use of the ECG to positively identify an individual.

The ECG of Twins

The incidence of twins in the United States is 1 in 86 pregnancies, with identical twins constituting 25 to 33%.[2] The ECG in normal twins (that is, those with no abnormalities) has been studied infrequently. The early report of Wise et al[3] in 1939 compared only the QRS in a study of 32 pairs of indentical twins (presumably monozygotic) and 18 pairs of nonidentical twins (dizygotic). Although more identical twins showed close similarity of tracings than did nonidentical twins (50% versus 22%), they did not find absolute correspondence in all identical twins as might have been expected. Mathers et al[4] and Preis and Srubarova[5] also found dissimilar ECGs more often in dizygotic than in monozygotic twins. Havlik et al[6] carried out a very limited study in 355 sets of middle-aged male monozygotic and dizygotic twins, examining only heart rate, P-R, QRS, and Q-T durations. They opined that there was genetically determined variability in ventricular rate and P-R interval. A case report in 1978[7] described a pair of identical twins, both having the Lown-Ganong-Levine form of preexcitation (short P-R interval and normal QRS complex) who had identical 12-lead ECGs. A careful and thorough study of ECGs in twins finally appeared in 1978.[8] There were 72 pairs of twins, 59 of which were monozygotic and 13 dizygotic. The investigators gave clear criteria for calling the tracings identical or different. The record of 1 twin was considered identical to that of the other twin when the frontal plane axis did not vary more than 10°, there was no more than 20% variation in duration of P, P-R, QRS, Q-T, and heart rate, there was no difference in polarity of S-T and T waves, and the same cardiac rhythm was present in both records. In the group of monozygotic twins, similar ECGs were found in 52% and dissimilar tracings in 48%. In the dizygotic twins 42% had similar tracings and in 58% the ECGs were different. Therefore, identical tracings are seen in both identical and nonidentical twins. This finding deserves considerable genetic investigation now that refined techniques can be applied to chromosomal and other features of twins. It is well known that exact zygosity is determined by careful examination of the placenta at birth or subsequently through comparison of physical characteristics, detailed blood typing, or possibly trial of tissue transplant from twin to twin.[1] Perhaps some twins in these various studies did not receive a full evaluation of zygosity. The subsets of twins with identical ECGs deserve full evaluation genetically.

Identification by ECG

There are times when identification of an individual must be done without the cooperation of or information from this person. An unconscious patient, a person unable to communicate because of loss of speech or a language barrier, and finally someone who has tried to hide his or her true identity by assuming a different personality and even different external physical characteristics—in all of these cases (and only if a previous ECG is available for comparison)—exact identification can be made by looking at the current and previous ECG. Fingerprints can be altered by a person wishing to hide his or her identity, but no one can alter the ECG. Thus, in crucial cases requiring exact identification of a person, the ECG offers primary information. Because it is becoming quite common to secure an ECG as part of many asymptomatic work-ups (preoperative, insurance, epidemiologic studies of communities and groups, and annual checkups), the likelihood of an individual having a tracing in his or her records is growing yearly.

In summary, one's ECG remains closely linked to, or even specific to, the individual. Identical twins, as presently defined, can have different ECGs. Furthermore, nonidentical twins, as presently defined, may have identical ECGs. We must determine if the criteria for identity in twins are correct. These electrocardiographic findings challenge the criteria used to determine whether a person is homozygous or heterozygous. Finally, the ECG perhaps can be considered a very stable identity marker of an individual.

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New Choices for the Initial Drug Therapy of Hypertension

NORMAN M. KAPLAN, MD

After their introduction in 1958, thiazide diuretics were soon found to be effective antihypertensive agents. As they were more widely used, they quickly became the initial drug chosen by most practitioners. Their place as the initial drug in a sequential, stepped-care approach was formalized in 1977 and reaffirmed in 1980 by the reports of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

The diuretic-first, stepped-care approach has been defended as both effective and safe. It has been used in all of the large-scale trials of the therapy of systemic hypertension, starting with the *VA Cooperative Study* in the 1960s[2] and proceeding to the *Hypertension Detection and Follow-Up Program* (HDFP) reported in 1979,[3] the *Australian trial* in 1980,[4] and the *Multiple Risk Factor Intervention Trial* (MRFIT) in 1982.[5]

The latter 3 trials involved mainly patients with "mild" hypertension, with diastolic blood pressure (BP) >90 mm Hg in MRFIT, from 90 to 104 in the HDFP, and from 95 to 109 in the Australian trial. These massive trials were needed for 2 reasons: first, patients with diastolic BP in the 90 to 104 mm Hg range comprise about 75% of the hypertensive population, perhaps 30 million Americans, so there is a great need to know if therapy is of value. Second, their rate of developing cardiovascular complications is relatively low so that many "patient-years" of observation were required to document the value of reduction of their BP. For various reasons, the results of these trials have not answered 1 of the critical questions: Does reduction of the BP prevent coronary heart disease, the major complication among hypertensive patients and the leading cause of death in the United States and other industrialized countries?

Let us examine the design and results of these 3 trials to better understand their implications for the therapy of patients with mild hypertension.

The 3 Trials

Hypertension Detection and Follow-Up Program: This trial proved that large numbers of hypertensive patients could be effectively managed to achieve a goal of diastolic BP <90 mm Hg. The study was designed to compare the effects on mortality rates of more intensive stepped-care drug therapy, provided in special clinics using various techniques to improve adherence, with the less intensive referred-care therapy, provided by community physicians using traditional practices. At the end of the 5-year study, those receiving more intensive care, the stepped-care group, had 26% fewer cardiovascular deaths and 13% fewer noncardiovascular deaths than did the less intensively treated referred-care group. As important as this study was in demonstrating the ability to manage large populations of mild hypertensive patients effectively, it was not designed as a straightforward trial of the efficacy of antihypertensive therapy.

Of those with mild hypertension who entered the trial with no antihypertensive medication and with no evidence of target organ damage, a 29% reduction in mortality rate was observed.[6] But that 29% figure should not be taken to indicate that 29% of the patients were saved. It represents a decrease in the 5-year mortality rate from 5.6% in the referred care group to 4% in the stepped care group. Thus, 5 years of more intensive drug therapy protected <2% of this population from death, a significant number but hardly 29% as some might infer.

Australian Trial: This trial was designed to test antihypertensive drug efficacy. Within 3 years of its start, those who received antihypertensive drugs (half of the sample) had 30% fewer cardiovascular complications (total endpoints) than those who received a placebo. The benefit was limited to patients whose diastolic BP remained >95 mm Hg during the study. Though the incidence of strokes, heart failure, and other cardiovascular complications was reduced, the number of heart attacks was not significantly reduced among the half that was treated with drugs.

Multiple Risk Factor Intervention Trial: This study enrolled men with high levels of overall risk: 62% were hypertensive, 64% were cigarette smokers, and their mean blood cholesterol level was 253 mg/dl. As in the HDFP trial, the enrollers were randomly divided into a more intensive, broad-based program to reduce the level of all 3 risks—the special intervention group and a usual care group followed by community physicians. Unfortunately for the trial, but fortunately for the patients, the usual care group received so much care that they had a much lower death rate than expected, a rate almost as low as the special intervention group.

Of those hypertensive patients who started with a diastolic BP >100 mm Hg, those more intensively treated had a lower rate of coronary and overall mortality; however, such protection was not provided in those who started with a diastolic BP from 90 to 94 mm Hg or in those with an abnormal resting electrocardiogram (Table I).

A possible explanation for the results: The results of these 3 trials, then, do not provide the hoped for ev-

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idence that more effective reduction of BP would reduce the incidence of coronary heart disease. One possible reason for this lesser effect may be the manner in which antihypertensive therapy was given, namely the diuretic-first, stepped-care approach. This cannot, however, be asserted with any degree of certainty. Because all 3 trials used a diuretic first in almost all treated patients, no comparison can be made of the effect of different drugs. Two trials comparing diuretics with beta-blockers are now in progress—1 in England and 1 in Sweden. Such evidence will be forthcoming, but not for some time.

The potential hazards of diuretics: In all 3 trials, about one third of the patients required a diuretic only to achieve the goal of therapy, and almost half received a diuretic plus a second-step drug. The possibility that the widespread use of a diuretic as first and often sole therapy could have decreased the protection from coronary events that was anticipated from lowering of BP is based on this premise: diuretics are now known to cause biochemical disturbances that increase cardiovascular risk, which could reduce the protection offered by the lower BP.[7]

These well-documented disturbances include an average decrease in serum potassium levels of 0.6 mmol/liter, an occasional worsening of glucose tolerance, and a 10 to 20 mg/100 ml increase in serum cholesterol levels. Other potential problems include an increase in plasma renin levels (related to a shrinkage of blood volume), increased blood viscosity, and an increase in plasma uric acid.

Of these changes, the ones that seem most likely to increase cardiovascular risks are the decrease in serum potassium levels and the increase in serum cholesterol levels. Hypokalemia may increase myocardial irritability, as was demonstrated in a study upon a group of hypertensive patients reported by Holland et al.[8] The patients were hypertensive with prior diuretic-induced hypokalemia. Their diuretics were stopped, and they were given enough potassium supplements to bring their serum potassium levels back to normal. At that time, they had no excess ventricular ectopic activity on 24-hour electrocardiographic monitoring. Diuretics were restarted, the serum potassium levels decreased again, and after 4 weeks another 24-hour monitor study was performed. Of the first 21 patients, 7 had significant increases in the frequency and severity of ventricular ectopic activity.

Although none of these patients had clinical manifestations of myocardial dysfunction, higher frequencies of life-threatening ventricular fibrillation in hypokalemic patients after acute myocardial infarction have been observed by others.[9,10] Thus, it may take an acute ischemic episode to uncover the potential hazard of hypokalemia upon myocardial irritability, possibly by a catecholamine surge which transfers potassium out of the plasma into cells, further reducing the plasma potassium level.[11] Patients who start with an abnormal electrocardiogram may be particularly susceptible to diuretic-induced hypokalemia. Recall the findings of the MRFIT study,[5] in which coronary deaths were higher in those hypertensive patients with abnormal electrocardiograms who were more intensively treated (Table I). Their therapy almost certainly included diuretics, but no specific information is now available about which drugs the individual patients were taking or the frequency of diuretic-induced hypokalemia among them.

TABLE I MRFIT: Mortality Rates in Hypertensive Patients Given Therapy

Initial BP (mm Hg)	Number		Coronary Deaths Per 1,000		Total Deaths Per 1,000	
	SI	UC	SI	UC	SI	UC
90–94	1,157	1,181	15	10	41	26
95–99	830	846	23	22	52	46
≥100	771	739	21	30	32	61
Normal ECG	2,785	2,808	16	21	36	43
Abnormal ECG	1,322	1,185	29	18	60	40

Synthesized from report of the Multiple Risk Factor Intervention Trial Research Group.[5]

BP = blood pressure; ECG = electrocardiogram; SI = Special Intervention; UC = Usual Care.

The potential risks of diuretic-induced increases of serum cholesterol levels are less acute and dramatic than those of hypokalemia. Not all have noted a significant increase after diuretic use and others have noted the increase to be only transient; however, many have documented a 10 to 20 mg/dl increase in serum cholesterol levels after weeks to years of diuretic therapy. It is likely to take many years for such an elevated cholesterol level to increase the degree of atherosclerosis, but the therapy of hypertension is obviously a prolonged process. By using the data from the Framingham study published in the American Heart Association's Coronary Risk Handbook, a persistent 10 to 20 mg/dl increase in serum cholesterol level will largely overcome the protection from coronary disease offered by a 10 to 15 mm Hg decrease in the BP. If such an increase in serum cholesterol level occurs with long-term diuretic therapy, lesser protection against coronary artery disease might be observed than would be predicted from the lowered BP.

Alternatives to diuretic-first stepped care: The evidence incriminating diuretics is largely circumstantial and should not be overdramatized. Millions of patients have taken diuretics for many years with no obvious trouble, and the resultant lowering of their BP has likely protected them from strokes, heart failure, progressive renal damage, and other hypertensive complications. More recently, hydrochlorothiazide was found to provide a greater antihypertensive effect than propranolol in black hypertensive patients, whereas the 2 drugs were comparable in whites.[12] But the potential atherogenic and arrhythmogenic hazards from diuretics should not be disregarded, particularly in view of the lesser protection shown against coronary artery disease in the trials that have used diuretics as initial and often sole therapy.

The use of diuretics as the first choice of therapy arose empirically: they were found to be effective and generally well tolerated. Moreover, when other nondi-

uretic drugs were used as initial therapy, fluid retention occasionally developed, causing their antihypertensive effectiveness to be largely lost. Such "pseudotolerance" due to fluid retention only served to strengthen the practice of using a diuretic first or in combination with the second-step drugs then available.

In the last few years, additional drugs have been introduced that cause less fluid retention and may therefore maintain their antihypertensive effectiveness without concomitant diuretic therapy. The *beta-blockers* were the first to be shown to work as monotherapy, except in the 20 to 30% of the hypertensive population who started off with low levels of plasma renin activity. Such patients were susceptible to fluid retention and some of them actually had paradoxical increases in BP when given beta-blockers alone.[13] There are, of course, adverse effects from beta-blockers that preclude their use in perhaps 25% of all hypertensive patients. In addition, a tendency for them to increase serum triglyceride levels and to lower the levels of the cardioprotective HDL-cholesterol has been recognized.[14]

Central alpha-agonists, including clonidine and guanabenz, are effective antihypertensives and may cause less fluid retention. The *peripheral alpha-antagonist* prazosin is a particularly attractive alternative; it usually does not cause the sedation so often seen with the centrally acting drugs, it can be used in those who are susceptible to problems from beta-blockade, and, unlike the beta-blockers, its use has not been accompanied by adverse effects on lipid levels.[15] Moreover, it lowers peripheral resistance—which is the hemodynamic fault in hypertension—unlike the beta-blockers which may increase peripheral resistance. Though tolerance has been observed with its use as an unloader in the treatment of heart failure, it has been shown to maintain its antihypertensive effect over 4 to 7 years.[16]

As we treat more and more mild hypertensive patients, who have relatively less risk from elevated BP itself, we need to be more cautious about potentially deleterious adverse effects from the therapies themselves. In view of the potential problems from diuretics, 1 or another of the currently available nondiuretic drugs may serve better as initial therapy. Although all of them may cause some problems, they should be considered as logical alternatives to the routine use of a diuretic as initial therapy. If they are used, even closer attention should be given to moderate sodium restriction, so as to reduce any tendency to fluid retention. Even so, if they fail to decrease the BP or if their effect is lost, fluid retention may be responsible, so that diuretics may then be needed. In addition, we should remember that many mild hypertensive patients can have the BP brought to safe levels by the judicious and enthusiastic use of nondrug therapies, including *weight reduction* for the obese and a moderate *restriction of dietary sodium intake* for all.

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The AJC in June 1958

CAROLE A. WARNES, MB, BS, MRCP and WILLIAM C. ROBERTS, MD

Radioactive Iodine for Angina Pectoris (Robert L. Segal, Solomon Silver, Stephen B. Yohalem, and Robert A. Newburger)

The concept of treating intractable angina pectoris by inducing hypothyroidism was first proposed in 1933 by Blumgart, Levine, and Berlin (*Arch Intern Med* 1933;51:866). The paper by Segal et al described 65 adults with angina pectoris "refractory to standard therapeutic measures." Each was given radioactive iodine (I^{131}) in doses sufficient to produce thyroid ablation and myxedema. After the development of hypothyroidism, 8 patients died within 3 months and the other 57 were followed 6 to 60 months. Of the 57 survivors, 15 became "essentially free of angina" ("excellent result"), 23 had "a significant reduction in frequency and severity of angina" ("good result"), 19 had some lessening of pain, remained unchanged, or had worsening of angina ("fair" or "poor" response).

Viewing the I^{131} treatment of angina from the current perspective shows that these reported studies were nonrandomized, nonblinded, and noncontrolled. Diagnosis before therapy and evaluation after therapy was entirely historical. The criterion for I^{131} treatment was that angina was "intractable" to medical therapy, which, of course, meant nitroglycerin. Whether some of those patients would have remained intractable had beta-blockers and calcium-channel blockers been available is unknown. Although I^{131} therapy of angina was based on the supposition that the hypothyroidism produced would diminish myocardial oxygen requirements, this hypothesis was never proven. Furthermore, although this therapy often decreased the severity and frequency of angina pectoris, at the same time it increased the serum cholesterol level, and thus probably accelerated the underlying atherosclerotic process. The benefit, therefore, was only short-term.

Treatment of Congenital Endocardial Fibroelastosis by Operative Poudrage (Raphael N. Paul and S. Gwin Robbins)

This report concerned 9 patients with primary endocardial fibroelastosis and 1 patient with anomalous origin of the left coronary artery from the pulmonary trunk. All 10, aged 4 to 24 months, were treated surgically by instilling sterile talc powder into the pericardial sac, the aim being to "stimulate the growth of new blood vessels." Preoperative diagnosis was based on the angiographic demonstration of a large, thick-walled, hypokinetic left ventricle and electrocardiographic and radiographic evidence of left ventricular hypertrophy. Four died early postoperatively, and the 6 survivors, followed for up to 3 years, were "clinically well" and had slight increases in weight curves.

Thus, this operation, which had only a theoretical basis, was performed in 10 children without objective follow-up criteria to determine success or failure. As with the I^{131} treatment for "intractable" angina, the operative treatment for presumed congenital endocardial fibroelastosis was both nonrandomized and noncontrolled, and its evaluation was nonobjective.

Acute Myocardial Infarction in a City Hospital in a 1-Year Period (264 Cases) (Monte Malach and Benjamin A. Rosenberg)

This report described 264 cases of acute myocardial infarction (AMI) seen at King's County Hospital, Brooklyn, New York, during a 1-year period (Table I). The duration of hospitalization varied from <1 hour to 80 days (mean 15 days); mortality was 47%! The criteria

TABLE I Clinical Features of Patients With AMI

Before AMI		
Age (yr)	32–97	(mean 68)
Male:female	162 (61%):102	(39%)
Smoking	56/96	(58%)
Angina pectoris	148/244	(61%)
Previous AMI	61	(23%)
Previous congestive heart failure	113/255	(44%)
Systemic hypertension	86/232	(37%)
Previous cerebrovascular accident	22	(8%)
Diabetes mellitus	69	(27%)
Digitalis treatment before AMI	57/246	(23%)
After AMI		
Rectal temperature >100°F	218	(82%)
Tachycardia (>100 beats/min)	74	(28%)
Enlarged heart by X-ray	61/138	(44%)
Congestive heart failure	137	(52%)

for inclusion included one of the following: (1) demonstration at autopsy of an AMI; (2) electrocardiographic demonstration (usually in a 12-lead tracing) of serial changes compatible with AMI; (3) a history suggestive of AMI without diagnostic or electrocardiographic changes, with a history of coronary artery disease followed by a temperature >100°F rectally or by leukocytosis >10,000 mm^3 or by elevation of the erythrocyte sedimentation rate, "not explainable by any other recognized disease."

These diagnostic criteria are obviously untenable in the light of current knowledge. The mortality of 47% appears alarmingly high, but this did not surprise the authors because of their patients' relatively older age, the high frequency of congestive heart failure, and the long delay before hospitalization. A significantly greater survival rate, however, was observed in those patients who received 50 mg daily of vitamin C—a study "randomized" by prescribing the vitamin to patients in alternate wards.

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Prescribing Information

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors of malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications**, **Warnings**, and **Precautions**.

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings**.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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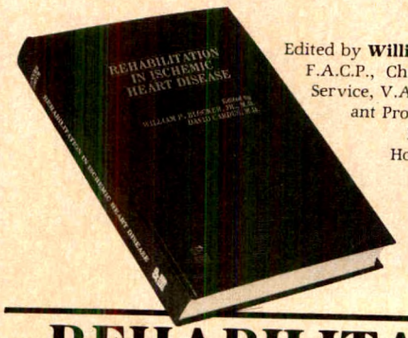

Edited by **William P. Blocker, Jr., M.D.**, F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine, Baylor College of Medicine, Houston, and **David Cardus**, M.D., F.A.C.C., Professor of Physiology and Rehabilitation, Baylor College of Medicine, Houston, Texas.

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Myocardial Reperfusion After Acute Occlusion of the Left Main Coronary Artery

Alessandro Salvi, MD
Silvio Klugmann, MD
Erica Della Grazia, MD
Patrizia Maras, MD
Fulvio Camerini, MD

Coronary recanalization with thrombolytic agents represents a new therapeutic approach to the treatment of acute myocardial infarction,[1] and previous experience suggests that patients with myocardial infarction and cardiogenic shock may benefit from this technique.[2]

A 58-year-old woman was admitted 30 minutes after the onset of persistent ischemic pain. Initial examination disclosed a moderately confused, pale, diaphoretic woman with a systolic arterial pressure of 80 mm Hg. Electrocardiography demonstrated sinus rhythm (62 beats/min), S-T segment elevation in leads I, aVL, and V_1 to V_4, with positive, high-voltage T waves in leads V_1 to V_6 and Q waves in lead aVL. Therapy with nitroglycerin (0.9 mg sublingually in 15 minutes), dopamine (7 μg/kg/min), and morphine sulfate (10 mg intravenously) was initiated without apparent effect on the clinical status. Lidocaine (3 mg/min intravenously, after a loading dose of 100 mg) was started and was continued throughout the procedure. Emergency coronary angiography (Judkins technique) to perform coronary recanalization was started 40 minutes after admission. By that time, femoral systolic arterial pressure had decreased to 60 mm Hg. On injection of contrast medium, an occlusion of the left main coronary artery was demonstrated (Fig. 1). Nitroglycerin (0.5 mg endocoronary) did not modify the angiographic appearance. Streptokinase (4,000 IU/min) was then infused through the Judkins catheter, and within 15 minutes patency was achieved in both the anterior descending and circumflex coronary arteries (Fig. 1). The infusion of streptokinase was maintained for 90 minutes employing a total dosage of 360,000 IU. Several episodes of ventricular tachycardia and ventricular fibrillation, treated with direct-current countershocks, took place during this period. At the end of the procedure the femoral arterial pressure was 104/65 mm Hg, ischemic pain had resolved, and sinus rhythm was present. Right coronary angiography, performed after lysis, demonstrated a wide, dominant artery with minimal luminal irregularities and no collateral vessels to the left coronary artery.

Postreperfusion electrocardiography demonstrated Q waves in leads I, aVL, and V_5 with reduced voltage R waves in V_1 to V_4, slight S-T segment elevation in leads aVL and V_8, and moderate S-T depression in leads II, III, and aVF.

Dopamine was discontinued within 24 hours and the patient was treated with heparin (25,000 to 35,000 IU/day), digoxin (0.25 mg/day), and lidocaine (2 to 4 mg/min) for 3 days. The subsequent clinical course was uneventful, the patient remained asymptomatic, and oral acenocoumarin was substituted for heparin therapy on the eighth day. An angiographic control on the 14th hospital day showed evidence of an isolated distal left main coronary artery stenosis of 60% diameter reduction. The left ventricle appeared slightly dilated (left ventricular end diastolic volume 97 ml/m²) with moderate hypokinesia of the anterolateral and septal walls. The ejection fraction was reduced to 0.45 and left ventricular end diastolic pressure was 20 mm Hg.

The patient underwent coronary artery bypass surgery on the 26th hospital day. The anterolateral left ventricular wall appeared akinetic but not fibrotic.

From the Department of Cardiology, University of Trieste, Trieste, Italy.
Manuscript received November 24, 1982; revised manuscript received February 14, 1983, accepted February 15, 1983.

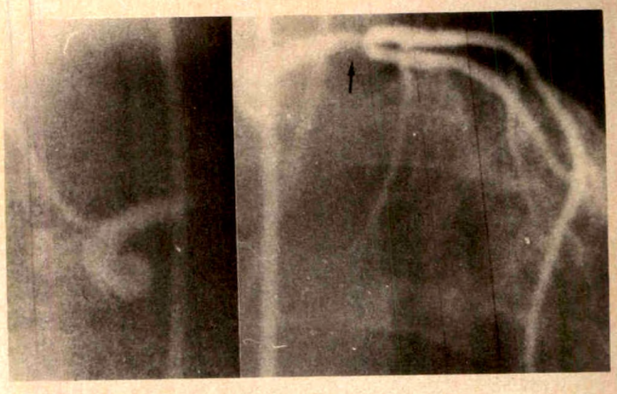

FIGURE 1. Left, left coronary arteriogram in the anteroposterior projection. Occlusion of the distal portion of the left main coronary artery. **Right,** left coronary arteriogram (same projection) 15 minutes after streptokinase infusion. Patency is achieved in both the anterior descending and circumflex coronary arteries with a residual luminal stenosis of 60% diameter reduction (**arrow**).

Only few cases of cardiogenic shock complicating acute myocardial infarction treated with intracoronary streptokinase have been reported.[2–5] Three showed a favorable response, but the thrombotic occlusion was never localized to the left main coronary artery. The case described suggests that a large amount of myocardium at risk was salvaged and therefore underlines the maximal potential therapeutic significance of the new technique of intracoronary thrombolytic infusion in acute myocardial infarction.

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Prinzmetal's Variant Angina Unresponsive to Calcium Channel-Blocking Drugs But Responsive to Combined Calcium Channel- and Beta-Blocking Drugs

Claude Bourmayan, MD
Jean Yves Artigou, MD
André G. Barrillon, MD
Alain Juillard, MD
Claude Fournier, MD
Jean Gay, MD
Alain Gerbaux, MD

The reputation of beta-blocking drugs at normal dosage in patients with spastic angina is so poor[1–3] that an aggravation of angina under such treatment suggests the diagnosis of spastic angina.[4] One case is described here showing that this reputation may not always be deserved.

On March 30, 1981, a 77-year-old man was admitted for spontaneous attacks of angina pectoris. The electrocardiogram during attacks showed the typical pattern of Prinzmetal's variant angina (Fig. 1). From March 31 to April 12, the patient had 11 spontaneous attacks of anginal pain, despite a dose-escalating calcium channel-blocking treatment that ended up as follows: diltiazem, 60 mg 4 times daily; nifedipine, 10 mg 4 times daily; and intravenous infusion of nitroglycerin (10 gamma/min). The failure of the calcium-channel blocking drugs led to the trial addition of 60 mg of propranolol per day to the treatment. This was thought useful because a marked increase in heart rate often occurred after the perception of pain. For 13 consecutive days, no attacks occurred (Fig. 2). The angina returned 48 hours after bradycardia (45 beats/min), and fatigue forced a reduction in propranolol to 40 mg/day (giving a propranolol serum concentration of 0.08 μmol/liter 4 hours after administration of 10 mg). During the 6 days of therapy with 40 mg of propranolol 4 attacks of angina occurred (Fig. 2). The treatment with 60 mg of propranolol was restarted (propranolol serum concentration 0.30 μmol/liter 4 hours after administration of 20 mg) and the patient complained of no pain until May 5, the day he left the hospital. Serum creatine kinase was always normal. After the same treatment when seen in November 1981 and 1982, he was found to have remained free of angina, and results of a Holter recording proved negative.

From the Centre de Soins Cardiaques Intensifs, Hôpital Boucicaut, 78 Rue de la Convention, 75730 Paris, cedex 15, France. Manuscript received January 17, 1983; revised manuscript received and accepted March 15, 1983.

The hypothesis of the effectiveness of the treatment with propranolol in this patient is based on the complete disappearance of anginal pain from the start of treatment until 48 hours after the dose reduction, and on the renewed cessation of pain after the return to the initial dosage. Although variant angina is well known to evolve capriciously,[5] the possibility of these findings being due to chance alone seems highly unlikely. Even though the 2 dosages of propranolol used were very close, their consequences on the heart rate were quite different; as soon as the dose reduction took place, the heart rate increased permanently from 45 to 60 beats/min. In addition, the serum concentration dosages differed widely, reaching the therapeutic zone (0.15 to 0.58 μmol/liter) when the patient was taking 60 mg/day and remaining well below it when he was taking only 40 mg/day. This beneficial effect may be explained by an acceleration of the heart rate during the anginal attacks, increasing from 57 to 75 beats/min during some anginal attacks. Poggi[6] also reported on 1 patient with variant angina successfully treated with propranol. This patient's heart rate increased from 68 to 80 beats/min during the anginal attacks.

Our case shows that propranolol administered at moderate doses can potentialize the effects of calcium channel-blocking drugs in an elderly subject with Prinzmetal's variant angina when there is sinus tachycardia during the anginal attacks. It would be worthwhile to test this hypothesis on a large number of patients.

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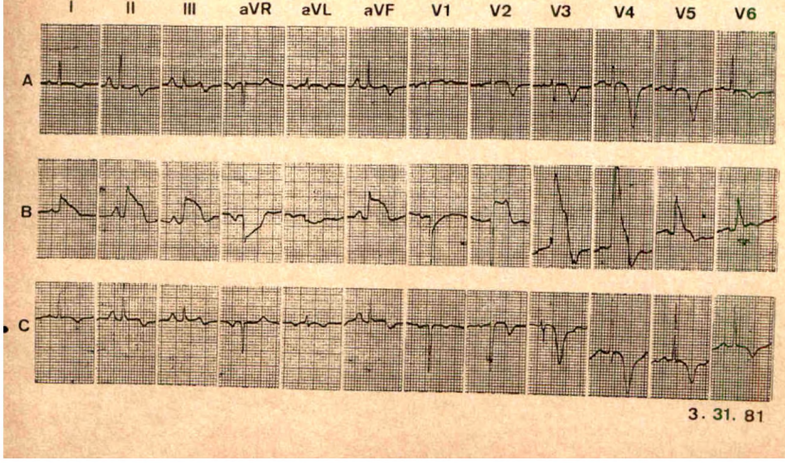

FIGURE 1. A, before the attack: symmetrical t-wave inversion from leads V_2 to V_6. **B,** during the attack: Prinzmetal's variant angina pattern with S-T elevation simultaneously in the anterior and diaphragmatic leads, associated with a heightening of the R wave. **C,** after resolution: return to initial tracing.

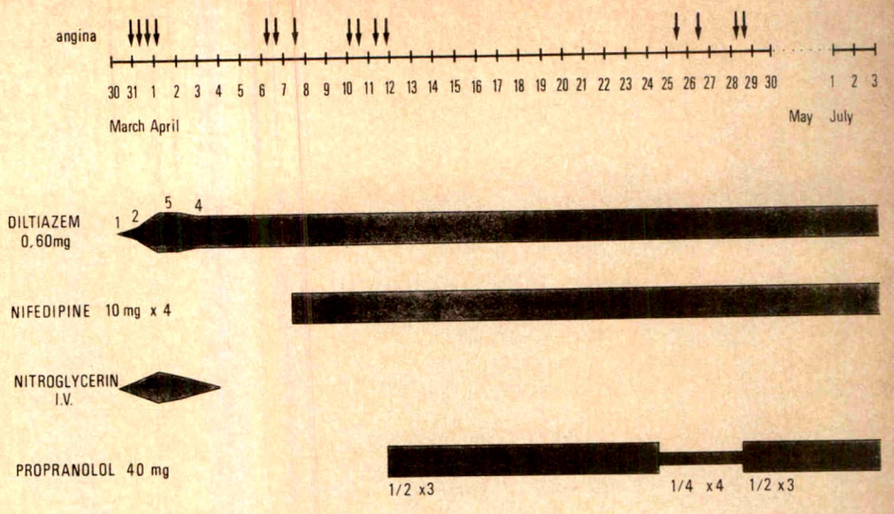

FIGURE 2. Top to bottom, anginal attacks (**arrows**), days, and different treatments with dosages: diltiazem, nifedipine, nitroglycerin administered by intravenous infusion (I.V.), and last, propranolol.

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Cysts in Left Atrial Myxomas Identified by Transesophageal Cross-Sectional Echocardiography

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Klaus Becker, MD
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Two-dimensional echocardiography performed from the thorax is the standard technique for the recognition of intracavitary cardiac structures. Two patients with left atrial myxoma are reported, in whom transesophageal cross-sectional echocardiography[1,2] revealed cysts within the tumors, a finding not observed by standard external approach. (The transthoracic echocardiograms were recorded with a 2.25 MHz transducer on a Diasonics 3400 R phased-array sector scanner. The same scanner was used for the transesophageal studies that were performed with a 3.5 MHz transducer.)

In a 59-year-old woman (Patient 1) transthoracic echocardiography revealed a left atrial mass the size of a plum which prolapsed into the mitral ostium in ventricular diastole. The mass was attached to the atrial septum and appeared homogeneous (Fig. 1). Transesophageal cross-sectional echocardiography revealed several isolated echolucencies within the mass (Fig. 2). Operation disclosed the mass to be a myxoma containing multiple cysts filled with serous fluid, measuring up to 10 mm in diameter (Fig. 3).

A similar finding was documented in a 65-year-old man (Patient 2). In the transthoracic cross-sectional echocardiogram, the tumor was seen in all 3 standard views, extending deep into the left ventricle in ventricular diastole (Fig. 4). Transesophageal cross-sectional echocardiography revealed a vast, mobile left atrial mass which was connected to the atrial septum by a small stalk. Several reproducible zones of echolucency with a maximum diameter of 10 mm was visualized within the tumor (Fig. 5). Examination disclosed a large tumor containing cysts filled with clear serous fluid (Fig. 6). Histologically, the tumor was a typical myxoma.

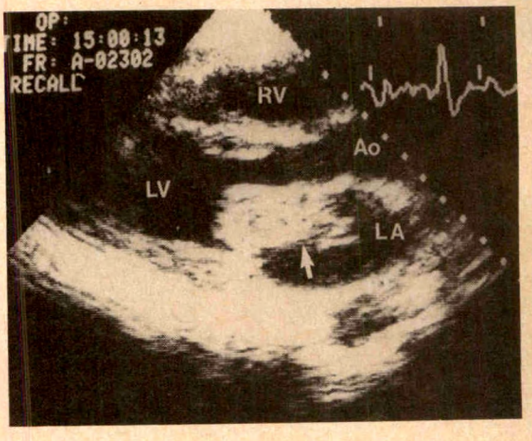

FIGURE 1. Transthoracic echocardiogram (parasternal long-axis view) from Patient 1, taken at end-diastole. The left atrial tumor (**arrow**) completely fills the mitral ostium. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

From the Departments of Cardiology, Cardiac Surgery, and Pathology, University Hospital Eppendorf, Hamburg, Federal Republic of Germany. Manuscript received December 21, 1982; revised manuscript received February 22, 1983, accepted February 25, 1983.

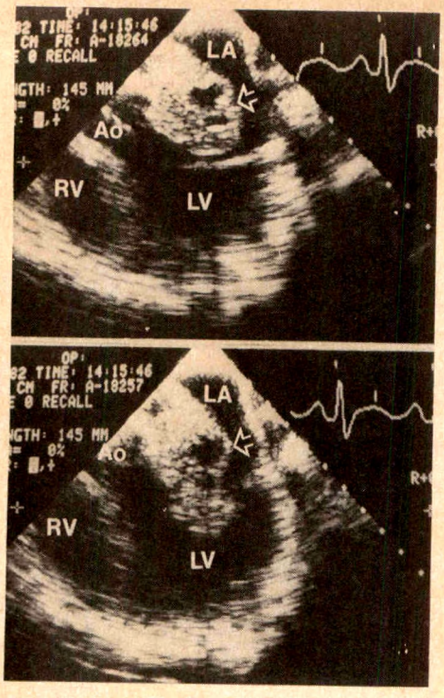

FIGURE 2. Transesophageal echocardiograms from Patient 1. **Upper panel,** frame taken at end-systole. **Lower panel,** frame was taken in diastole when the left atrial tumor mass is seen to extend into the left ventricle. Both frames show 2 areas of echolucency within the tumor (**arrows**). Abbreviations as in Figure 1.

Apart from an echocardiogram described by Come et al[3] and a recent brief report on tumor hemorrhages in atrial myxomas,[4] regions of echolucency within cardiac tumors have not been reported. Despite thorough searching for cysts from the standard external views (parasternal long- and short-axis, apical 4- and 2-chamber, subcostal long- and short-axis), we could identify the cysts only with the transesophageal approach. This fact is probably related to the vicinity of the esophagus and the left atrium, to the different cross-sectional planes obtainable, and to a lesser extent, the higher frequency of the transesophageal probe.

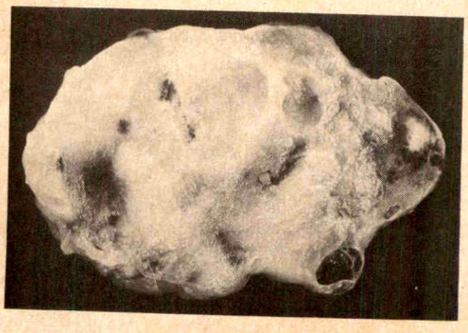

FIGURE 3. Section through the tumor specimen from Patient 1, showing several cysts that correspond to the echolucencies noted on the transesophageal echocardiograms.

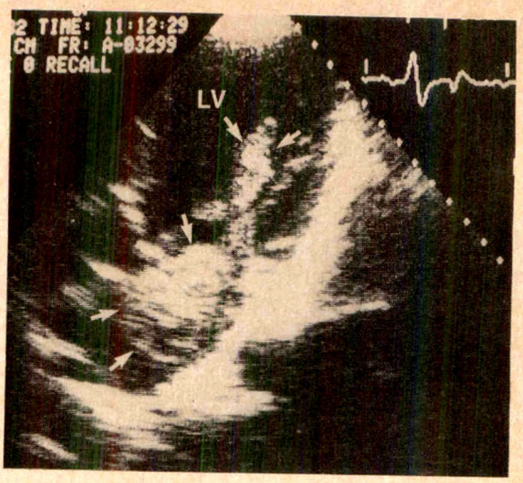

FIGURE 4. Apical 2-chamber view (right anterior oblique equivalent) from Patient 2. The contour of the left atrial myxoma is marked by **arrows.** This end-diastolic frame shows an extension of the tumor reaching into the left ventricle (LV).

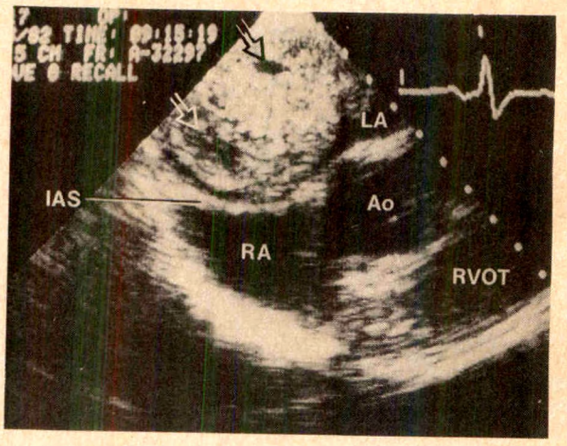

FIGURE 5. Transesophageal echocardiogram from Patient 2. The tumor fills nearly all of the left atrium in this view. Two cysts are marked by **arrows.** IAS = interatrial septum; RA = right atrium; RVOT = right ventricular outflow tract; other abbreviations as before.

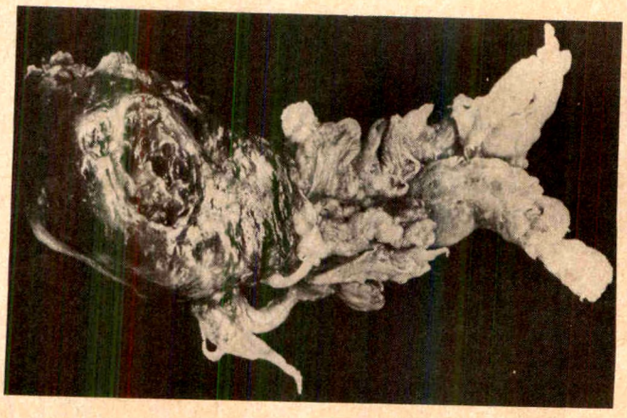

FIGURE 6. Resected tumor from Patient 2. The section through the tumor base shows 2 cysts. The villiferous surface of the distal part of the tumor is obvious.

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Structural Changes in Ventriculoaortic Porcine Valved Conduit Implanted in a Child

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The implantation of a left ventricular (LV) apicoaortic composite conduit is a well-established procedure for the relief of severe LV outflow obstruction.[1,2] Although the use of valve-bearing conduits in the right side of the heart seems to be limited by a high rate of early obstruction, the fate of the left-sided ones is poorly known and rarely pathologically documented.

A 15-year-old boy was admitted for surgical repair of severe aortic stenosis. At operation, the calcified and hypoplastic aortic valve was excised, but the small diameter of its anulus (17 mm) prevented the insertion of a prosthesis. The aortic outflow was closed by a Dacron ® patch, and a Hancock composite conduit was inserted between the LV apex and the ascending aorta. There was prompt postoperative recovery.

The patient was asymptomatic for 2 years, when exertional dyspnea and fatigue appeared. Cardiac catheterization confirmed the presence of severe aortic regurgitation. No pressure gradient was measured across the conduit. Angiocardiography showed marked regurgitation of the conduit valve and moderate mitral regurgitation. Reoperation was performed 26 months after the first operation. The mitral valve, which appeared diffusely calcified, was replaced with a #29 Sorin tilting-disc prosthesis; the Hancock conduit was excised and replaced with another Dacron conduit containing a #21 Sorin prosthesis. The patient died from infective complications 14 days later. The excised conduit was slightly bent at the aortic extremity and its inner surface was partially lined by fibrous tissue (Fig. 1); the porcine valve cusps were torn and calcified (Fig. 2).

LV apicoaortic porcine conduits are being implanted in an increasing number of young subjects.[1,2] To date, dysfunction of such conduits has been reported in only 3 cases.[3,4] In a recent multicenter study,[3] 227 children were evaluated as late survivors of porcine valve replacement; in 20, the valve degenerated. Eight patients in this series received an apicoaortic conduit; in 1, both valve and conduit were removed because of valve calcification. Chen et al[4] described the clinicopathologic findings in 2 patients in whom an apicoaortic porcine conduit was excised due to degeneration. In both, the porcine valve was severely calcified and deformed. The case reported here confirms that porcine valves in LV apicoaortic conduits behave like heterografts inserted in the aortic position. Thus, when implanted in children,

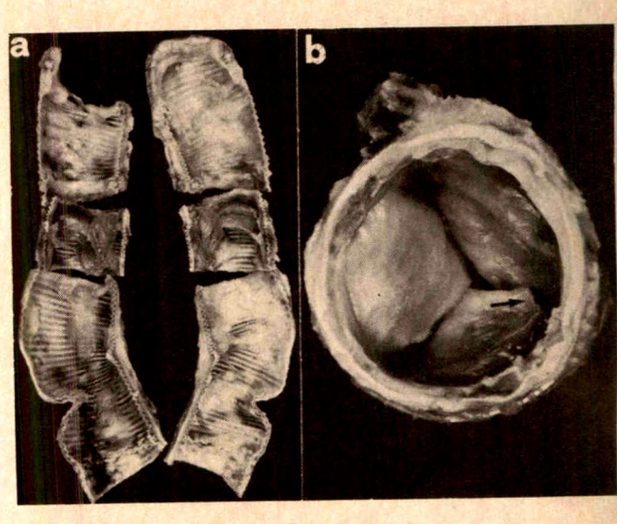

FIGURE 1. a, gross appearance of the explanted conduit. Its inner surface is lined by a thin, nonobstructive fibrous peel. **b,** view of the explanted Dacron conduit valve which was severely incompetent due to a torn commissure (**arrow**); no gross calcific deposits are evident.

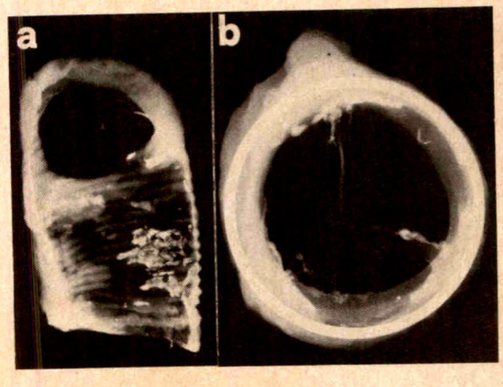

FIGURE 2. a, roentgenographic examination of the explanted Dacron conduit: note the presence of scattered calcific deposits. **b,** roentgenogram of the conduit porcine valve which demonstrates fine calcification at the commissure and base of the cusps.

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they are prone to calcify like those inserted in either the mitral and aortic position.[5]

The fate of the Dacron tube of a composite conduit seems to depend on which side of the heart it is inserted. In conduits used for reconstruction of the right ventricular outflow, formation of a fibrous "peel" has been observed, progressively thickening as the result of the thrombus organization between the peel and the conduit wall.[6] In our patient, the inner surface of the left-sided conduit appeared lined with a calcified but thin, nonobstructing peel, most likely because in this position the high velocity of the bloodstream prevents thrombus formation and organization.

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Noninvasive Diagnosis of Interrupted Inferior Vena Cava: Gated Pulsed Doppler Application

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Interruption of the inferior vena cava (IVC) with drainage by way of the azygous system is an uncommon lesion frequently associated with complex intracardiac anomalies. Comprehensive imaging of this vascular anomaly requires direct visualization of the isolated intrahepatic caval segment and discrimination of the azygous system from other vertical vascular channels, such as the thoracoabdominal aorta and anomalous pulmonary venous communications.[1] Recognition of this anomaly before cardiac catheterization avoids unnecessary wire and catheter manipulation and attendant irradiation. This report illustrates the combined use of 2-dimensional (2-D) and gated pulsed Doppler echocardiography for noninvasive identification of interruption of the IVC with hemiazygous continuation.

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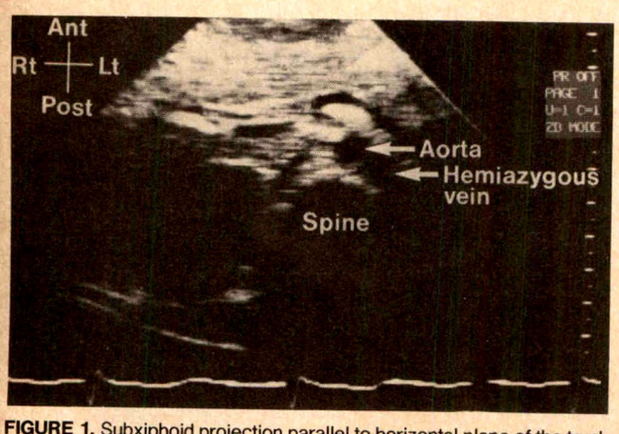

FIGURE 1. Subxiphoid projection parallel to horizontal plane of the trunk demonstrating the aorta and posterior hemiazygous contination of the infrarenal vena cava. Ant = anterior; Inf = inferior; Lt = left; Rt = right; Sup = superior.

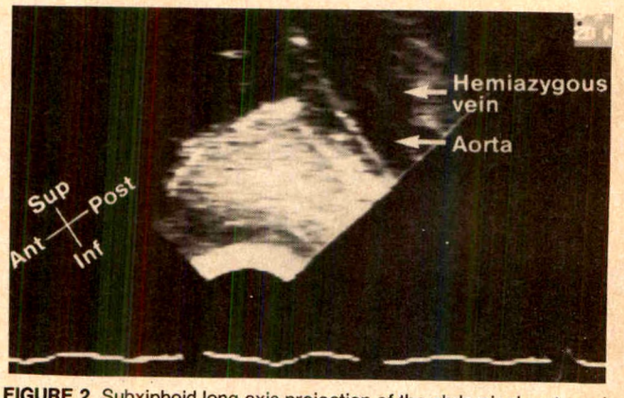

FIGURE 2. Subxiphoid long-axis projection of the abdominal aorta and hemiazygous vein parallel to the sagittal plane of the trunk. Ant = anterior; Inf = inferior; Post = posterior; Sup = superior.

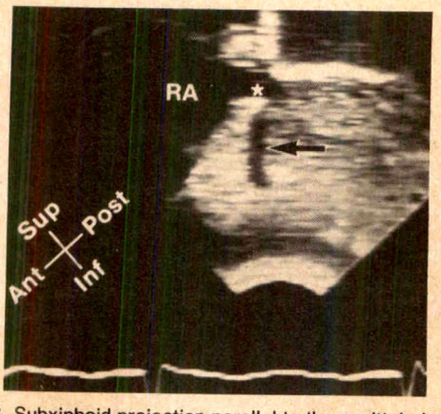

FIGURE 3. Subxiphoid projection parallel to the sagittal plane of the trunk demonstrating the hepatic segment of the inferior vena cava receiving the hepatic veins and entering the right atrium (RA). The infrahepatic suprarenal segment of inferior vena cava is absent. The **arrow** indicates the hepatic veins; the hepatic vena cava is indicated by an **asterisk.** Abbreviations as in Figure 2.

A 5-year-old girl had a known ventricular septal defect with mild pulmonary artery hypertension. The infradiaphragmatic systemic venous return was evaluated by combined 2-D and gated pulsed Doppler echocardiography. A left-sided suprarenal continuation of the IVC was demonstrated by subxyphoid projections parallel to the horizontal and sagittal planes of the trunk[2,3] (Fig. 1 and 2). Projections parallel to the horizontal plane of the trunk displayed the left-sided suprarenal hemiazygous continuation of the IVC posterior to the abdominal aorta (Fig. 1). Orthogonal projections parallel to the long axis of the trunk identified contiguous left-sided vertical vascular channels adjacent to the lumbar spine (Fig. 2), and isolated hepatic segment of IVC receiving hepatic veins (Fig. 3). The left-sided vertical channels were identified by branching patterns, that is, celiac and superior mesenteric arteries, and gated pulsed Doppler spectral wave forms. Doppler examination of the more anterior vertical channel revealed the typical wave form of the descending aorta (Fig. 4). Examination of the posterior vascular channel (Fig. 5) demonstrated a low frequency

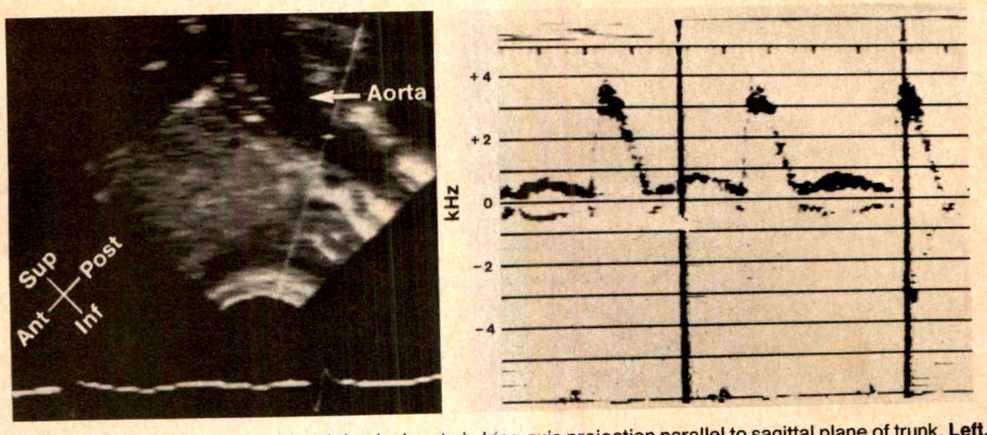

FIGURE 4. Gated pulsed Doppler examination of the abdominal aorta in long-axis projection parallel to sagittal plane of trunk. **Left,** sample volume in aorta; **right,** aorta gated pulsed Doppler wave form. Abbreviations as in Figure 2.

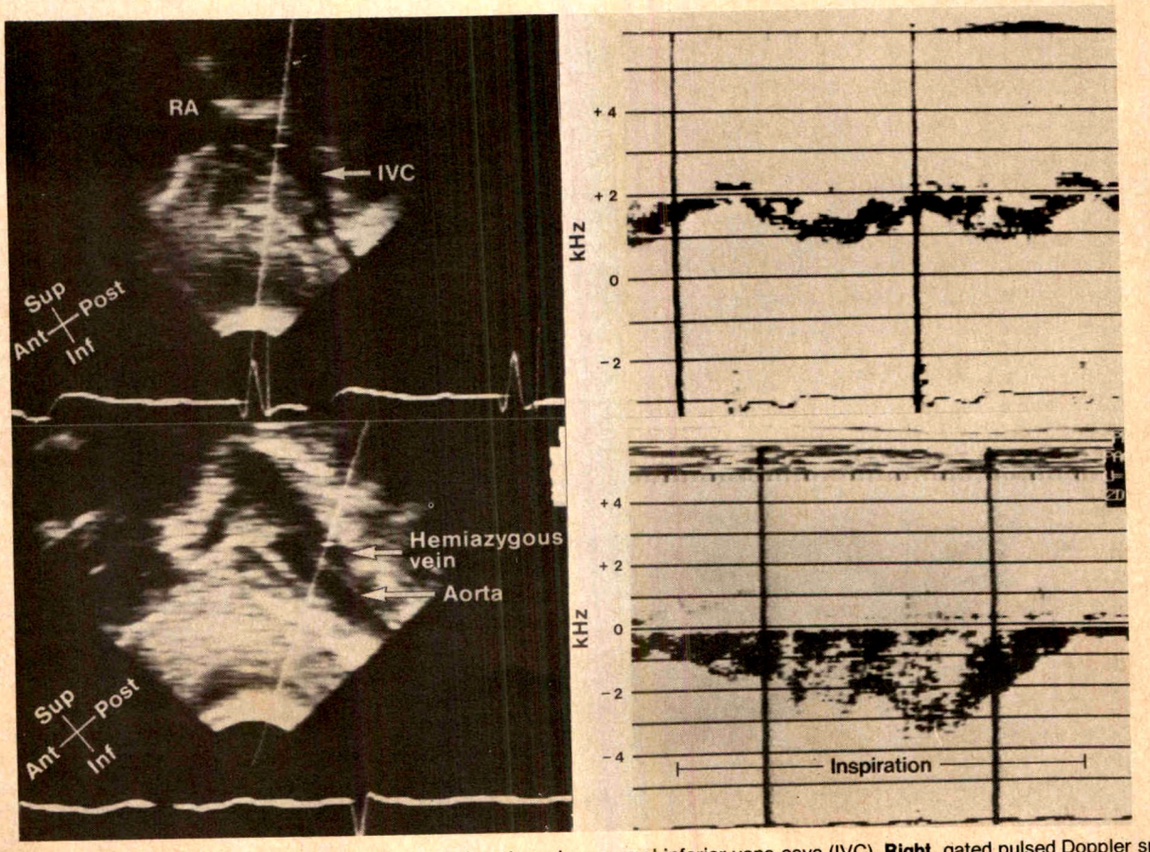

FIGURE 5. Upper panels: Left, gated pulsed Doppler sample volume in a normal inferior vena cava (IVC). **Right,** gated pulsed Doppler spectral wave form of normal inferior vena cava. **Lower panels: Left,** gated pulsed Doppler sample volume in hemiazygous vein. **Right,** gated pulsed Doppler spectral waveform in hemiazygous vein demonstrating pan-inspiratory acceleration of venous blood. Abbreviations as before.

broad band spectral distribution with inspiratory acceleration.

The combination of the 2-D echocardiographic anatomic detail and gated pulsed Doppler flow characteristics facilitate identification of vascular structures in the thorax and abdomen. The proximal abdominal aortic branches, that is, celiac and superior mesenteric arteries, and renal veins are landmarks for localization of the suprarenal segment of the IVC. In situs solitus, the left renal vein junction with the IVC marks the superior extent of the infrarenal IVC.[4] Absence of the IVC between this caval-renal vein junction and the hepatic vein confluence and the presence of a left-sided hemiazygous continuation identifies suprarenal IVC interruption. The resultant contiguous vertical thoracoabdominal vessels, left-sided aorta and hemiazygous vein, also may be identified by their distinctive gated pulsed Doppler flow characteristics. The pulsatile wave-form of the thoracoabdominal aorta (Fig. 4, right) is distinguishable from the heterogeneous low frequency wave form of the central systemic veins (Fig. 5, top right). The central venous Doppler wave form is influenced by the intrathoracic pressure variation and manifests baseline variation with the respiratory cycle.

In conclusion, interruption of the IVC with hemiazygous extension is demonstrated by the absence of continuity between the IVC at the level of the left renal vein and the hepatic segment of vena cava. The hemiazygous continuation is established by its direct visualization and its distinctive gated pulsed Doppler flow characteristics.

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Congenital Absence of Pulmonary Valve Associated With Tetralogy of Fallot: Diagnosis by 2-Dimensional Echocardiography

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Congenital absence of the pulmonary valve is a rare cardiac malformation usually associated with tetralogy of Fallot.[1] This syndrome usually presents early in life and is characterized by cyanosis, a to-and-fro precordial murmur, and frequently respiratory distress.[1] This report describes 2-dimensional (2-D) echocardiographic findings in 2 newborns with absent pulmonary valve in association with tetralogy of Fallot.

Case 1: *A full-term newborn boy was seen at 1 day of age because of cyanosis. A to-and-fro 3/6 systolic and diastolic murmur was heard at the left sternal border. The electrocardiogram gave normal results. The thoracic roentgenogram showed mild cardiomegaly and a normal pulmonary vasculature. A right cineventriculogram revealed a ventricular septal defect with an overriding aorta, large pulsating pulmonary arteries, a narrowed pulmonary valve anulus, and no evidence of pulmonary valve tissue except for a concentric ridge of tissue at the expected site of the pulmonary valve (Fig. 1).*

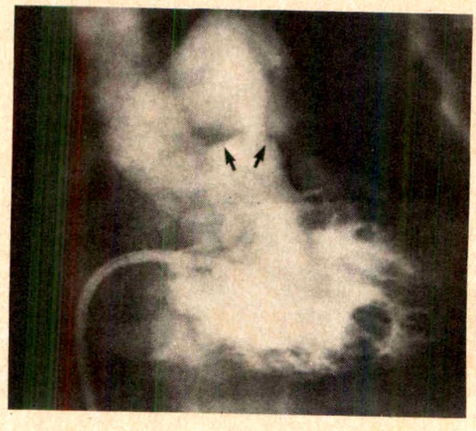

FIGURE 1. Case 1. Right cineventriculogram in anteroposterior projection. The aorta and pulmonary artery are simultaneously opacified. A concentric ridge of nonmobile tissue (**arrows**) is seen at the pulmonary anulus which contributes to stenosis of the tract. The pulmonary artery is markedly dilated.

Two-D echocardiography was performed at 1 day of age with a mechanical sector scanner (Smith-Kline) using a 30° 5-MHz transducer. An overriding aorta, subaortic ventricular septal defect, and dilated pulmonary arteries were demonstrated. At the expected site of the pulmonary valve, 2 ridges, each 2 mm thick, with markedly decreased mobility were seen. Ventricular septal motion was normal (Fig. 2).

Case 2: *A full-term newborn boy was referred because of cyanosis. A 3/6 harsh systolic and diastolic murmur at the lower left sternal border was heard. Bilateral rales and rhonchi were present over the lungs. The liver was palpable 4 cm below the right costal margin. The electrocardiogram showed right atrial enlargement. The thoracic roentgeno-*

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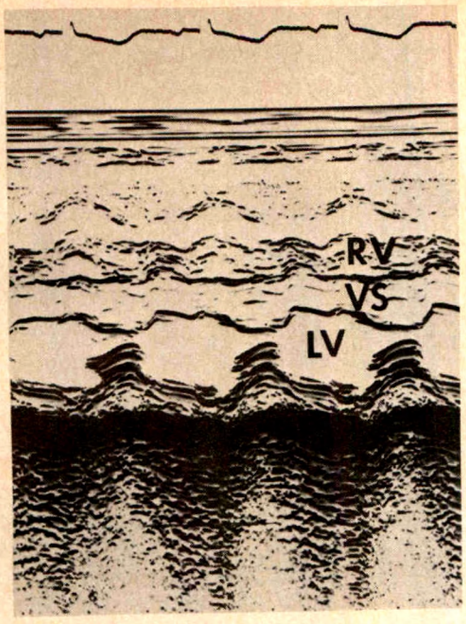
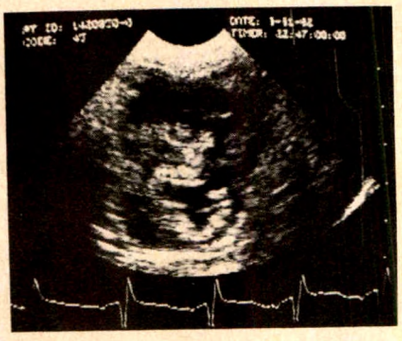


FIGURE 2. Case 1. M-mode recording of the right and left ventricles at the level of the mitral chordae. Normal ventricular septal motion is demonstrated. Echoes within the right ventricular cavity are reflected from the tricuspid valve supporting apparatus. LV = left ventricle; RV = right ventricle; VS = ventricular septum.

gram showed moderate cardiomegaly and enlarged pulmonary arteries. Right ventricular cineangiography showed a hypertrophic right ventricle and a narrowed pulmonary valve anulus. The aneurysmal dilatation of the right pulmonary artery was so marked as to impinge on the left atrium. Pulmonary valve leaflets were not identified.

Two-D echocardiography was performed at 1 day of age with an Advanced Technology Laboratory mechanical sector scanner using an 80° 5-MHz transducer. In contrast to the findings in Case 1, a large mass of muscle continuous with the mid- and lower portion of the ventricular septum was present at the right ventricular apex. The large mass of muscle attached to the ventricular septum appeared to extend into the right ventricular outflow tract. Multiple bright echo-reflecting areas were recorded within the ventricular myocardium (Fig. 3). Similar to Case 1, thick ridges at the pulmonary valve anulus extended for 2 to 3 mm into the lumen of the pulmonary artery (Fig. 4). These structures did not move. The main, right, and left pulmonary arteries were markedly dilated. Ventricular septal motion was normal. A subcostal 4-chamber view demonstrated what appeared to be a continuous "membrane" transecting the left atrium (Fig. 5). Although this initially suggested the diagnosis of cor triatriatum, short-axis angulation of the transducer demonstrated that the posterior chamber was continuous with the main pulmonary artery and represented the right pulmonary artery.

At 2 days of age, 24 hours after cardiac catheterization, the patient died. At autopsy, trabeculation of the ventricular septum was present as previously identified on the 2-D



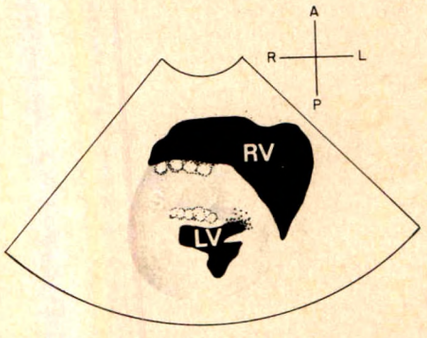
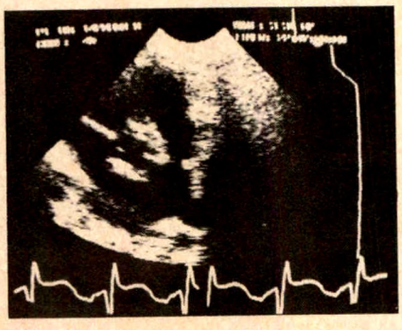


FIGURE 3. Case 2. Parasternal short-axis 2-dimensional echocardiogram and corresponding schematic drawing. The ventricular septum appears thick because of large trabeculations on the right ventricular aspect. Multiple bright echo reflecting areas (**arrows**) of myocardial calcification are seen in the ventricular septum. A = anterior; L = left; LV = left ventricle; P = posterior; R = right; RV = right ventricle; S = ventricular septum.



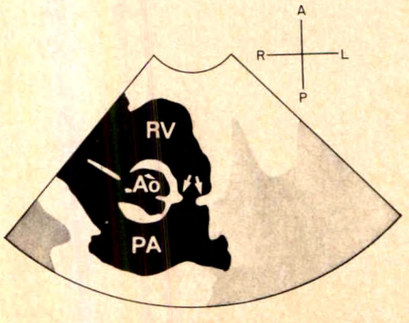


FIGURE 4. Case 2. Parasternal short-axis 2-dimensional echocardiogram obtained in a plane superior to that of Figure 3 and corresponding schematic drawing. Two ridges (**arrows**) represent the rudimentary pulmonary valve causing stenosis of the tract. The main and right pulmonary arteries are markedly dilated. A = anterior; Ao = aorta; L = left; P = posterior; PA = pulmonary artery; R = right; RV = right ventricle.

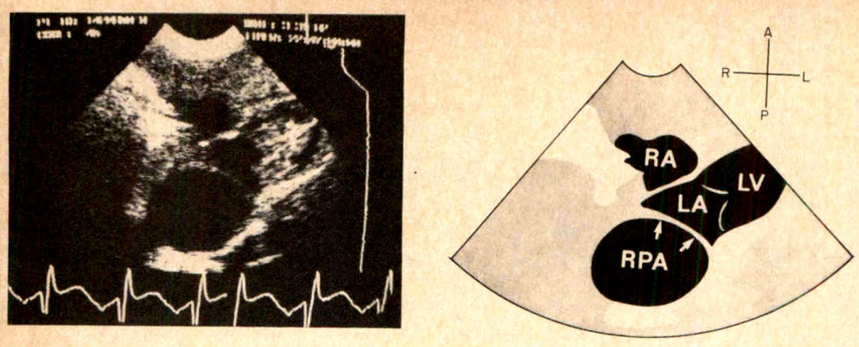


FIGURE 5. Case 2. Subcostal "4-chamber" 2-dimensional echocardiogram and corresponding schematic drawing. The aneurysmal right pulmonary artery impinges on the left atrium and mimics cor triatriatum. A = anterior; L = left; LA = left atrium; LV = left ventricle; P = posterior; R = right; RA = right atrium; RPA = right pulmonary artery.

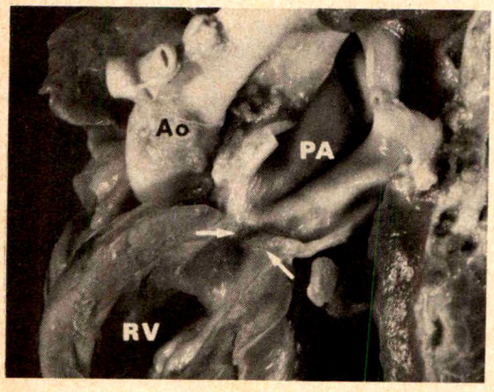


FIGURE 6. Case 2. Specimen of the heart showing opened right ventricle and pulmonary artery. The pulmonary valve is absent. At the pulmonary anulus a circumferential ridge (**arrows**) of fibrous tissue is present. The pulmonary anulus is narrowed. Main and right pulmonary arteries are aneurysmally dilated. Ao = ascending aorta; PA = pulmonary artery; RV = right ventricle.

echocardiogram. A well-developed crista supraventricularis slightly obstructed the infundibulum. The pulmonary valve was replaced by a continuous fibrous ridge inserted on a stenotic anulus which measured 1.5 cm in circumference (Fig. 6). Marked dilatation of the main and right pulmonary arteries was present. The right pulmonary artery impinged on the left atrium and compressed the right main stem bronchus. Multiple calcified foci were present in the myocardium including the ventricular septum.

In each of our 2 patients with absent pulmonary valve, the 2-D echocardiogram demonstrated marked enlargement of the pulmonary arteries and the presence of thick ridges instead of fully developed pulmonary valve leaflets. The echocardiographic image of the dysplastic and rudimentary pulmonary valve elements was best shown in the short-axis view at the left sternal border. The ridges extended a few millimeters into the lumen of the pulmonary artery and did not have the typical motion of a pulmonary valve leaflet.

A few reports have dealt with echocardiography in congenital absence of the pulmonary valve[2–4] in tetralogy of Fallot. Cheatham et al[4] reported on 9 infants with tetralogy of Fallot and absent pulmonary valve, in 6 of whom 2-D echocardiograms were obtained. These investigators suggest that echocardiographic findings of abnormal interventricular septal motion, right ventricular dilatation, aneurysmal dilatation of the pulmonary arteries, and overriding aorta appear to be unique echocardiographic features of this syndrome.

The limitations of suggested echocardiographic criteria and possible diagnostic pitfalls are exemplified by our own cases. Although many features described by Cheatham's group were present in our 2 patients, neither infant had abnormal ventricular septal motion, although marked pulmonary regurgitation was apparently present in our Case 2. Moreover, the presence of calcium in the ventricular myocardium of this patient suggests the possibility that he may have had cardiac failure with myocardial necrosis in utero secondary to severe pulmonary regurgitation.

Of particular interest, the dilated right pulmonary artery in Case 2 impinged on the left atrial wall. This pathologic change caused a peculiar appearance of the 2-D echocardiographic subcostal 4-chamber view. On this view, the left atrium appeared to be partitioned by a membrane yielding an echocardiographic image mimicking that of cor triatriatum.[5] However, the absence of a fenestration in the "membrane" and the demonstration that the posterior "chamber" was, in fact, the right pulmonary artery led to the correct diagnosis.

Thus, a precise image of the anatomic features of congenital absence of the pulmonary valve in tetralogy of Fallot can be obtained by 2-D echocardiography. Our cases demonstrate that one cannot confidently rely on the presence of abnormal septal motion to suggest the diagnosis of absent pulmonary valve in tetralogy of Fallot. The echocardiographic diagnosis should rely on the direct demonstration of all the anatomic lesions, including the appearance of ridges at the pulmonary anulus representing rudimentary pulmonary valvular tissue.

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False Aneurysm of Mitral-Aortic Intervalvular Fibrosa: Diagnosis by 2-Dimensional Contrast Echocardiography at Cardiac Catheterization

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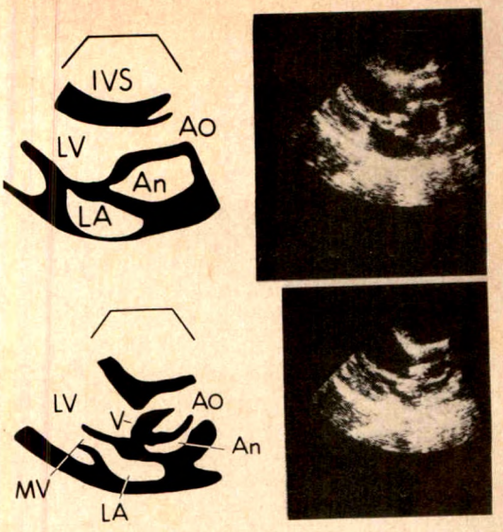

FIGURE 1. Parasternal long-axis view shows the aneurysmal sac (An) as an echo-free space between the posterior aortic wall (Ao) and the left atrium (LA). The aneurysm appears to increase in size during systole (**upper panel**) and to decrease in size during diastole (**lower panel**) as shown by the simultaneously recorded electrocardiogram. A large aortic valve vegetation (V) prolapses into the left ventricle (LV) during diastole (**lower panel**). The anterior leaflet of the mitral valve (MV) has an abnormal bulge at the base present during diastole (**lower panel**). IVS = interventricular septum.

False aneurysm of the mitral-aortic intervalvular fibrosa may occur as a complication of aortic valve infective endocarditis.[1] These aneurysms may rupture causing death, may develop thrombi that may embolize, and may cause detachment of the aortic or mitral valve.[1,2] Accurate and early diagnosis is important for successful surgical therapy. We describe a patient in whom the diagnosis was made before surgery by contrast 2-dimensional (2-D) echocardiography.

A 28-year-old man had symptoms of night sweats for 6 weeks. Aortic systolic ejection and early diastolic murmurs (both grade 3/6) were heard; an S_3 gallop was present. Blood cultures grew group D enterococcus; he was treated with intravenous ampicillin and gentamicin. On 2-D echocardiography, a large aortic valve vegetation was seen prolapsing into the left ventricle. A large aneurysmal sac was present between the posterior aortic wall and the left atrium, which expanded during systole (Fig. 1, upper panel) and decreased during diastole (Fig. 1, lower panel). The left ventricle was dilated. Peripheral venous 2-D contrast echocardiography was unremarkable. At catheterization, right heart pressure and blood oxygen saturation were within normal limits. The presence of severe aortic regurgitation was confirmed. Contrast 2-D echocardiography, performed through the intracardiac catheter, demonstrated that the aneurysmal sac filled from the left ventricle and not from the aorta, and no mitral regurgitation was seen (Fig. 2). The origin of the aneurysm, demonstrated by 2-D contrast echocardiography, was later confirmed by cineangiography. During surgery, the aortic valve was bicuspid and extensively destroyed by vegetation. The ostium of the false aneurysm measured 2 × 2 cm and was located beneath the aortic valve noncoronary cusp in the fibrous continuity between the mitral and aortic valves. The false aneurysm extended onto the superior aspect of the left atrium, ending in a blind pouch. The mitral valve was normal. The opening of the false aneurysm was closed and the aortic valve replaced with a bioprosthesis. Postoperative echocardiography showed the region of the aneurysm to be indistinct, probably because of thrombus formation. Contrast echocardiography performed through the left atrial line showed no filling of the false aneurysm by the contrast material, confirming the security of the surgical closure.

Aneurysms of the mitral-aortic intervalvular fibrosa are due to the spread of infection from the aortic valve. The intervalvular fibrosa attaches to the aortic root and to the anterior leaflet of the mitral valve. Perforation from infection in this area may cause an aneurysm to develop in the epicardial tissue between the aorta and

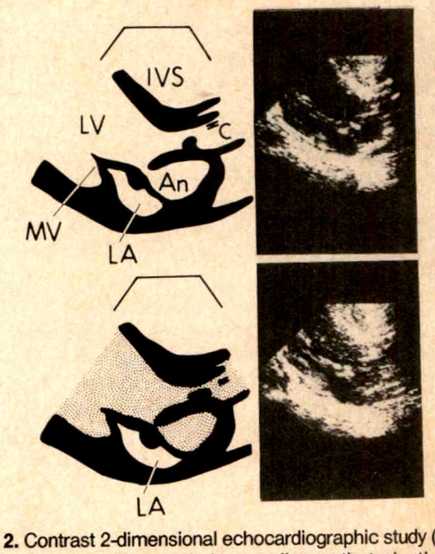

FIGURE 2. Contrast 2-dimensional echocardiographic study (parasternal long-axis views) performed during cardiac catheterization with the catheter (C) positioned in the aortic root (**upper panel**). The left ventricle (LV) filled with contrast during the first diastolic interval after injection. The aneurysm (An) then filled with the first systole after injection (**lower panel**). No contrast material is seen in the left atrium (LA). IVS = interventricular septum; MV = mitral valve.

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left atrium which is in direct communication with the pericardial space.

Angiographic studies have been the standard method for detecting these aneurysms. However, precise definition of structures by angiography is difficult because the left ventricular outflow tract may be obscured by overlapping contrast-filled structures. In addition, the number of views is limited by the amount of contrast material that can be used in an individual patient. In our patient, contrast 2-D echocardiography was useful (1) to define that the aneurysm originated from the left side of the heart, (2) to demonstrate that the aneurysm filled from the left ventricle, and (3) to confirm obliteration of the aneurysm postoperatively. Two-dimensional echocardiography was particularly helpful because of the added spatial orientation. An echo-free space lying between the posterior aortic root and the left atrium expanded during systole. Contrast 2-D echocardiography was then used to define its relation to the intracardiac chambers. Our case, the first to describe an aneurysm of the mitral-aortic intervalvular fibrosa by 2-D echocardiography, demonstrates the usefulness of contrast 2-D echocardiography during cardiac catheterization in defining this "complex" cardiac lesion.

Acknowledgment: We acknowledge with gratitude the technical assistance of Michael Butler.

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Platypnea and Interatrial Right-to-Left Shunting After Lobectomy

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Platypnea is dyspnea in the upright position relieved in the supine position. This unusual symptom has been reported after pneumonectomy due to a new onset of right-to-left shunting through a previously unrecognized atrial septal defect or a patent foramen ovale in the absence of pulmonary hypertension.[1–5]

A 63-year-old man presented with cough and hoarseness. X-ray disclosed a mass in the lower lobe of the right lung, and aspiration biopsy disclosed adenocarcinoma. Right lower lobectomy was performed. He was readmitted to the hospital 4 months later for dyspnea. Electrocardiography revealed sinus tachycardia and nonspecific ST-T changes. At pulmonary angiography which was negative for emboli, the 7F pigtail catheter slipped repeatedly into the left atrium. It was apparent that the patient was dyspneic and cyanotic only when erect and was comfortable in the supine position. Arterial blood gases on 40% oxygen were: pH 7.42, partial pressure of carbon dioxide 29 mm Hg, partial pressure of oxygen 81 mm Hg in the supine position, and 7.44, 25 mm Hg, and 44 mm Hg, respectively, in the upright position. On 100% oxygen, partial pressure of oxygen was 56 mm Hg. The diagnosis of right-to-left shunt was made conclusively by contrast echocardiography. Boluses of 10 ml of saline solution were injected into the right atrium. Contrast echoes appeared in all 4 cardiac chambers only when the patient was in the sitting position (Fig. 1). Right-sided cardiac catheterization was performed (Table I). Oxygen saturation measurements (Table I) revealed a significant right-to-left atrial level shunt only in the upright position. The systemic-to-pulmonary flow ratio (Qs/Qp) was 2.1. Because the patient was confined to bed, being dyspneic and cyanotic only in the upright position, percutaneous closure of the defect was attempted using an umbrella prosthesis. The umbrella failed to fix to the atrial septum and migrated into

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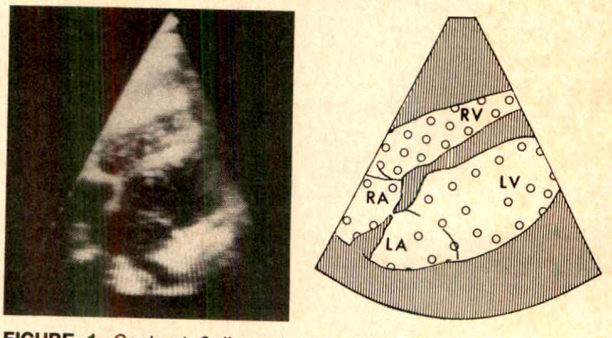

FIGURE 1. Contrast 2-dimensional echocardiogram, subcostal 4-chamber view. The **circles** indicate contrast material appearing in all 4 chambers after injection into the superior vena cava. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

TABLE I Hemodynamics

	Supine	Sitting
Pressures (mm Hg)		
Right atrium (mean)	4	2
Right ventricle	20/3	17/2
Pulmonary artery	20/10	17/7
Pulmonary artery wedge	10	7
Oxygen saturations (%)		
Mixed venous	68	62
Pulmonary artery	69	64
Pulmonary vein	98	98
Radial artery	94	80
Qs/Qp	1.2	2.1

the left ventricle. Median sternotomy was performed. The heart and mediastinum were shifted to the right, but there was no compression on the cardiac chambers. A patent foramen ovale, which could be stretched to a diameter of 2.5 cm, was found. The umbrella prosthesis was extracted from the left ventricle and the atrial septal defect was closed. The patient did well postoperatively with the disappearance of platypnea and orthostatic cyanosis (on 100% oxygen the partial pressure of oxygen was 436 mm Hg in the upright position).

Five cases of new-onset interatrial right-to-left shunting after left or right pneumonectomy for carcinoma of the lung have been reported previously. A few months after pneumonectomy, each patient developed dyspnea, worse in the upright position. Although right-sided cardiac catheterization confirmed the diagnosis of right-to-left shunt, none of the patients had hemodynamic measurements in the upright position. At thoractomy a patent foramen ovale or a secundum type atrial septal defect was found and repaired, resulting in symptomatic relief. Our patient developed platypnea and orthostatic cyanosis after only lobectomy. Shunting was present only in the upright position and pulmonary hypertension was absent. New onset right-to-left shunting after pneumonectomy is rare. We suspect that the condition is probably more common than recognized because the shunt may be present only in the upright position. Physical examination and arterial blood gas studies performed in the supine position may be within normal limits. Our patient is the first reported with platypnea after only lobectomy in the presence of normal upright pulmonary arterial pressure. This condition can be diagnosed noninvasively and corrected surgically with complete symptomatic relief to the patient. The pathophysiologic aspects of this condition are poorly understood.

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FAMILIAL AGGREGATION OF CORONARY HEART DISEASE AND ITS RELATION TO KNOWN GENETIC RISK FACTORS

Ten Kate et al[1] are to be congratulated for a thoughtful study on the relevance of family history, exclusive of traditional risk factors, to coronary heart disease (CAD). We recently examined this issue from a slightly different perspective and reached similar conclusions: that there is something related to family history and yet *not* tightly related to epidemiologically oriented risk factors which increases the risk of CAD.

We studied 204 men before angiography, characterizing them on a host of signs, symptoms, and risk factors.[2] We examined the association of these risk factors with the angiographically determined extent of CAD and then followed our patients for 1 year to determine the relation between risk factors and subsequent morbidity. As ten Kate et al noted, we found that a family history of heart disease (defined as onset of CAD in a parent or sibling before age 60) was of significant importance in predicting subsequent cardiac morbidity.[3] However, a family history of heart disease had an interesting relation to vessel disease per se. When we excluded the men free of significant CAD, we examined what risk factors might predict severe extensive CAD versus less extensive CAD in the remaining 171 patients. Family history alone was significantly associated ($p < 0.05$) with extensive CAD; no other risk factor bore a relation to extensive CAD.[4] With multiple regression analysis, the most important variables associated with extensive CAD were family history, age, smoking, and cholesterol (listed in declining order of importance).

These findings lend further support to ten Kate's findings that although there is a virulence associated with a family history of CAD, the pathophysiology of such a relation remains unclear.

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* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

COMPRESSION OF THE SUPERIOR VENA CAVA AND RIGHT ATRIUM IN CARDIAC TAMPONADE

We read with interest the article by Miller et al,[1] which carefully depicts the static (abnormal right atrial contour) and dynamic (caval compression) angiographic features in patients with pericardial tamponade. The finding of right atrial (RA) collapse by 2-dimensional echocardiography was particularly striking. However, our impression was that the latter finding was not specific for tamponade. Therefore, we retrospectively reviewed 22 consecutive echocardiographic studies on patients with moderate- or large-sized pericardial effusions. Clinical findings were reviewed as to the presence or absence of clinical tamponade (tachycardia >120 beats/min, hypotension and pulsus paradoxus >20 mm Hg). Echocardiographic studies were reviewed specifically as the size of the effusion, tachycardia, swinging motion, "a" kick dependent right ventricular (RV) filling,[2] RV compression (<5 mm), accentuated RA or left atrial (LA) wall motion with atrial systole ("a") and RA collapse, as described by Miller et al. The findings are shown in Table I.

We would, therefore, like to supplement the findings of Miller et al with the following: (1) RA collapse appears to be a sensitive sign for tamponade, but it lacks specificity in that it was present in 5 of 13 large effusions without tamponade, (2) RA collapse must be differentiated carefully from visualization of wall motion during atrial systole, which is common and due to the wall being "freed-up" by the effusion, (3) pericardial fluid behind the left atrium with visualization of LA systole is also common in large effusions (9 of 15 patients), and (4) as previously sited, "a" kick dependent RV filling appears to be the more specific sign for tamponade.

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REPLY: It is important to note that the 2-dimensional echocardiographic findings included in our report were drawn from a specifically selected group of patients with cardiac tamponade and, as such, cannot be used to define either the sensitivity or specificity of RA inversion as a marker of this hemodynamic phenomenon. These patients were simply included to further elucidate the mechanism of the reported angiographic phenomenon and to demonstrate that this same finding can be observed using a noninvasive imaging method. Although our patients were clearly selected for the presence of tamponade and therefore cannot be used to assess sensitivity or specificity, it is likewise clear that one cannot define the specificity with sufficiently narrow confidence intervals to distinguish an estimated 77% (10 of 13) specificity for RA "a" kick from an estimated 62% (8 of 13) specificity for RA collapse when these estimates are based on a study which includes only 2 true-positive cases. However, the observation of Pinero et al is useful for the design of future prospective studies.

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TABLE I Findings in a Retrospective Review of 22 Consecutive Echocardiographic Studies

	Number of Patients With Findings						
Size	Tachycardia	Swinging	"a" Kick Dependent RV Filling	RV Compression	LA "a"	RA "a"	RA Collapse
Moderate (n = 7)	0	2	0	0	0	2	0
Large (n = 13)	8	10	0	0	7	3	5
Large with tamponade (n = 2)	2	2	2	1	2	2	2

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Currently available antianginal agents...
and how they are most appropriately employed as

BASIC THERAPY FOR THE PREVENTION OF ANGINA PECTORIS*

Report from "Step-Care Therapy for Ischemic Heart Disease"
—a special symposium preceding the annual meeting
of the American College of Cardiology, April 24, 1982.

Synopsis of the Symposium

Step 1: Nitrates

Since nitrates both reduce myocardial oxygen demand and increase myocardial oxygen supply, their use is warranted as initial therapy for the control of angina pectoris. Dosage needs often vary significantly from patient to patient, and attention should be given to ensure that an adequate dosage level has been established.

Step 2: Nitrates and beta blockers

For angina refractory to maximum-dose nitrate therapy, the complementary actions of beta blockers and nitrates provide a rational therapeutic modality. At this point a beta blocker should be added to the nitrate regimen.

Step 3: Nitrates and calcium antagonists

Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

Nitrates are basic in step-care therapy for ischemic heart disease

Step 1
Stable or unstable angina: Nitrates

Step 2
If not controlled: Nitrates + beta blockers

Step 3
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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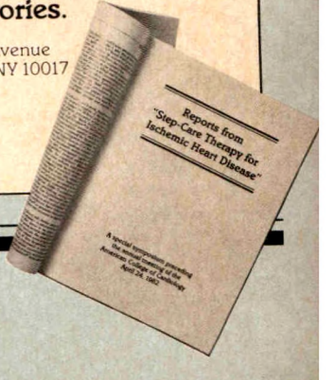

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*ISORDIL has been evaluated as probably effective when taken by the sublingual or chewable route and possibly effective when taken orally for this indication. See Brief Summary on following page.

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*Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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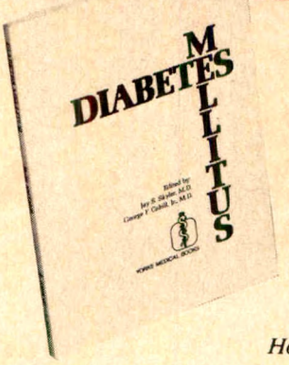

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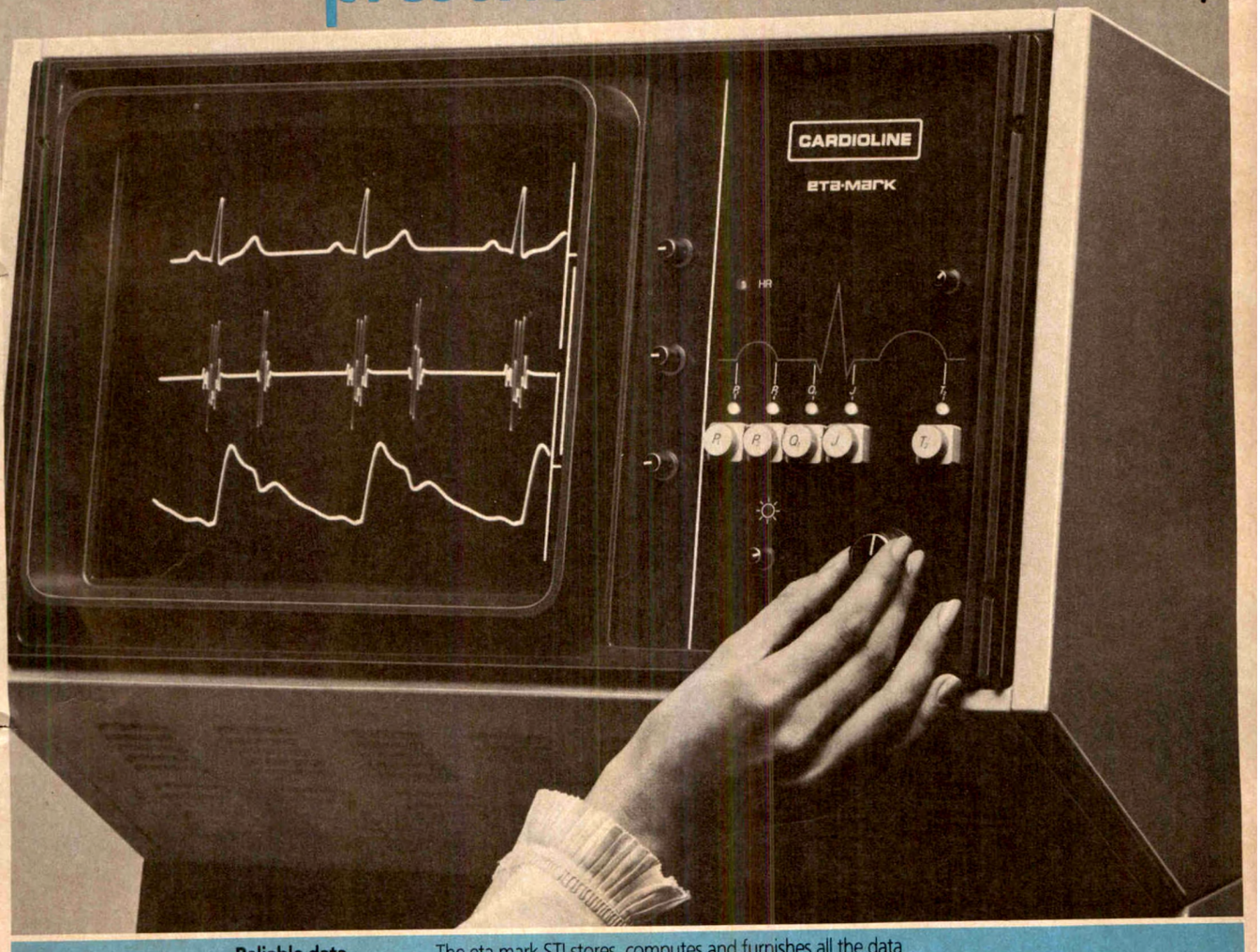

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A THERAPEUTIC STEP AHEAD

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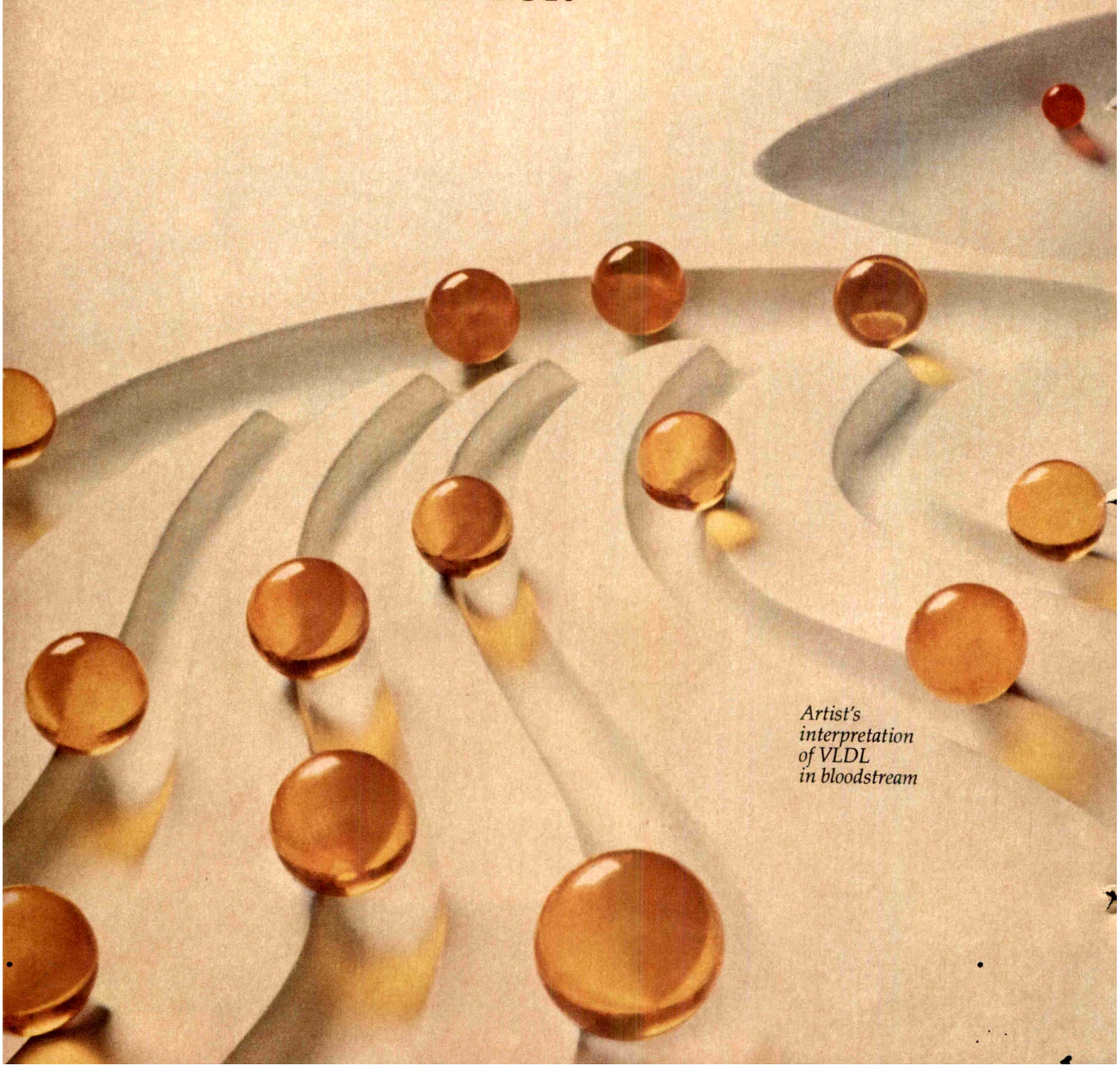
MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

Favorably regulates the balance of lipid fractions in certain dyslipidemias:

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transport cholesterol to the liver for catabolism and excretion)

LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

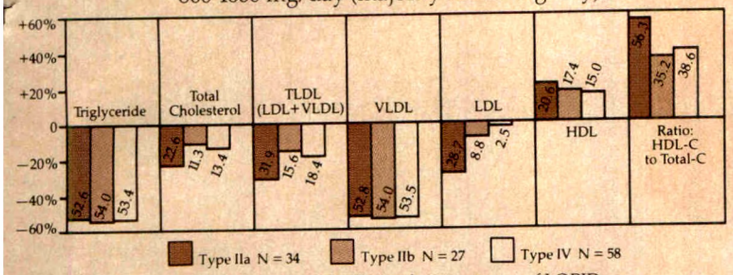


Artist's interpretation of VLDL in bloodstream

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.
†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:
1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

LOPID® 300-mg capsules
(gemfibrozil)

PARKE-DAVIS

Please see following pages for brief summary of prescribing information.

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LOPID®
(gemfibrozil)
A LIPID REGULATOR

LOPID® (gemfibrozil) Capsules

Before prescribing, please see full prescribing information.
A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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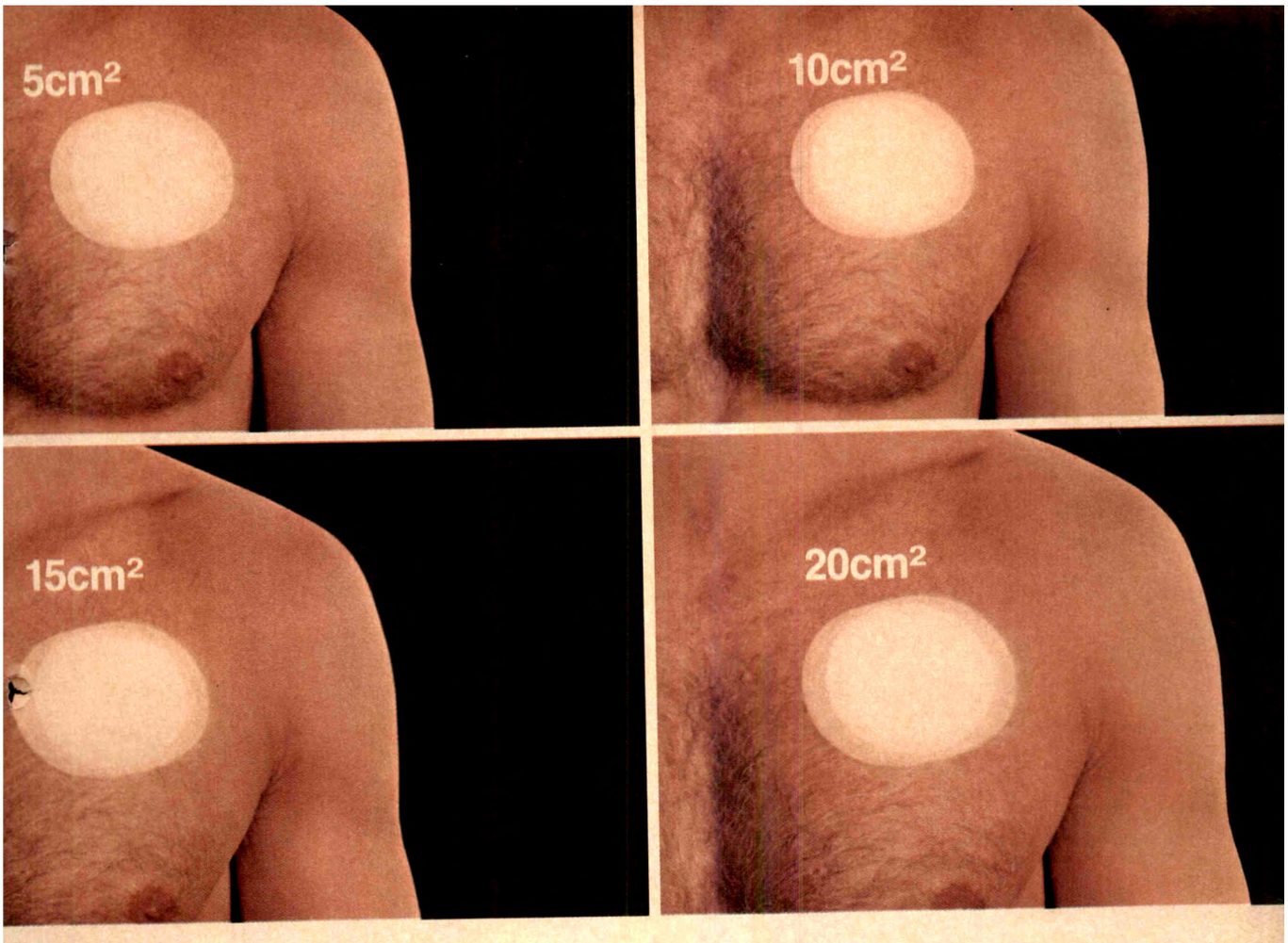

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Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

The most widely prescribed transdermal nitroglycerin system.

Please see next page for a summary of prescribing information.

Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release in vivo of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

[1]Data on file: Key Pharmaceuticals, Inc. 01/83

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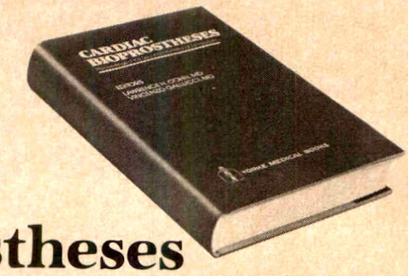

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

Almost 20 years have gone by since the first reports of homograft valve replacement by Drs. Donald Ross and Brian Barratt-Boyes and almost 10 years since the first reports began to appear about commercially available, quality-controlled porcine bioprosthetic and bovine pericardial valves. This book brings you completely up-to-date on what has happened since and what is happening *today*.

If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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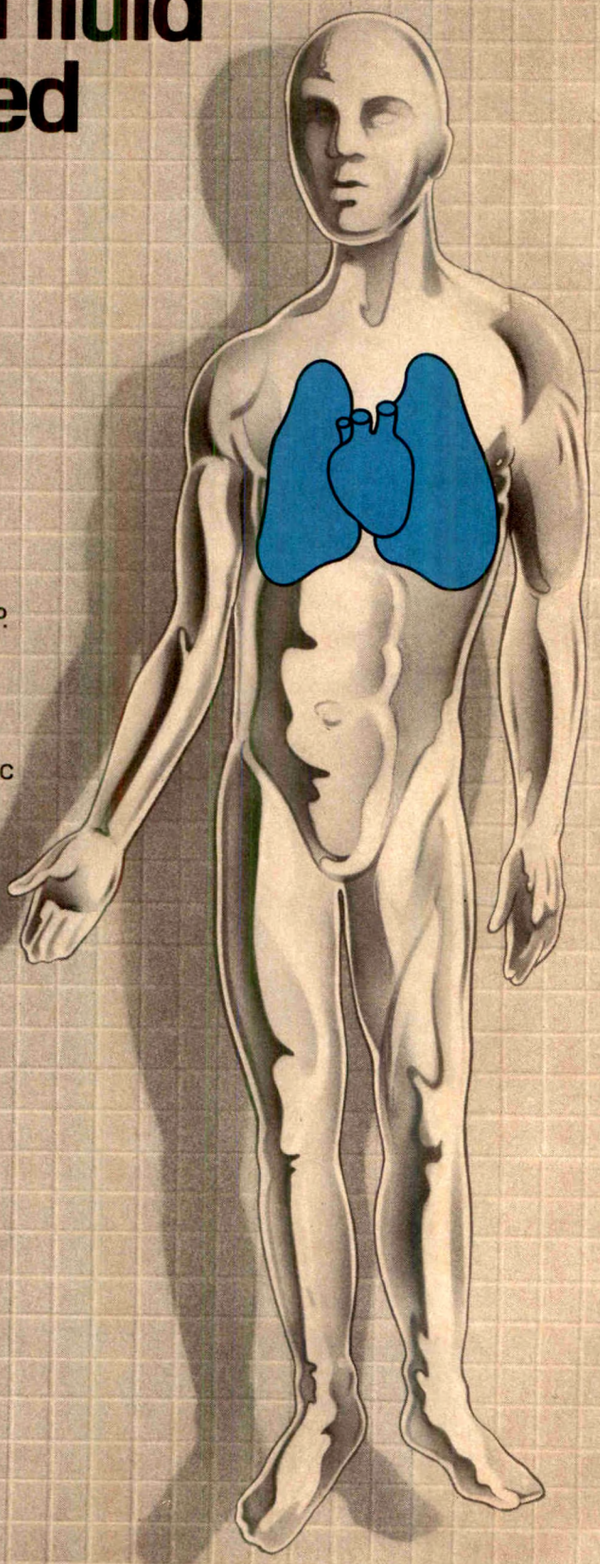
Therapeutic challenge:

Redistribution of fluid in CHF associated with acute MI



In Early CHF[1]

Pulmonary congestion with increased preload.

Findings: Elevated preload, elevated blood pressure, normal or slightly decreased cardiac output, PCWP greater than or equal to 18 mm Hg.

Therapeutic goal:
Reduce pulmonary congestion, lower PCWP to 15 to 18 mm Hg.

In Late CHF[1]

Pulmonary congestion with increased preload and afterload.

Findings: Low cardiac output, depressed blood pressure, and high PCWP.

Therapeutic goal:
Reduce pulmonary congestion, preload, and afterload, increase cardiac output, and lower PCWP to 15 to 18 mm Hg.

Why wait for the patient to become unresponsive to traditional diuretic/digitalis therapy?

1. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356-1362, 1404-1413.

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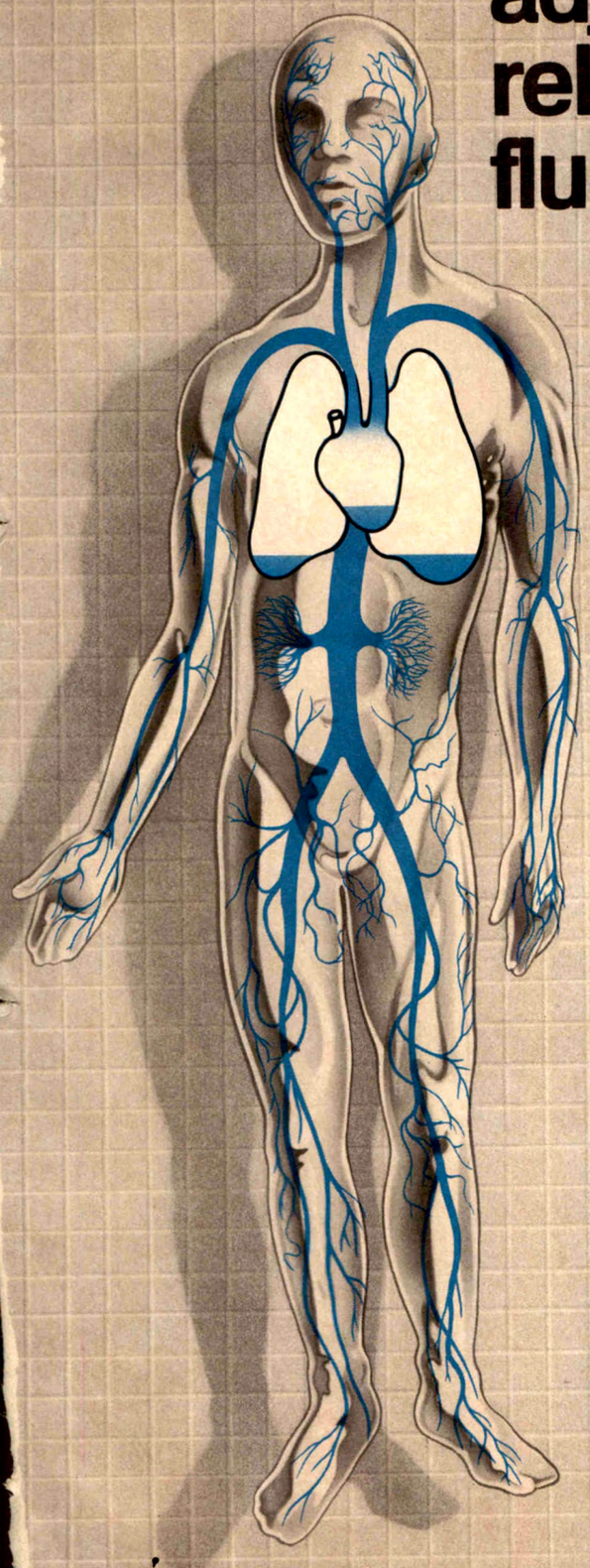
Give Tridil® (nitroglycerin) adjunctively to help relieve the fluid-burdened heart



In a dose-related manner, Tridil produces dilation of both arterial and venous beds—for a therapeutic redistribution of fluid.

Suggested therapy in early CHF

If blood pressure is normal:
Tridil to reduce preload and PCWP. Diuretics to decrease fluid volume.

If blood pressure is elevated:
Tridil should be initiated immediately to decrease preload, PCWP, and blood pressure, while maintaining coronary perfusion.

Suggested therapy in late CHF

If blood pressure is normal or only moderately depressed:
Vasopressors and Tridil adjunctively, with continuous hemodynamic monitoring.

If blood pressure is significantly depressed:
Vasopressors and Tridil adjunctively to reduce preload, afterload, and PCWP. Dopamine to increase the contractility of the myocardium. PCWP should be monitored.

Use of nonabsorbing Tridilset®

Sorptive loss of Tridil may range up to 80% when infused through a conventional PVC administration set[2] To overcome this problem, administer Tridil through Tridilset administration set or Tridilset V.I.P.™ volumetric pump connector set.

The most frequent adverse reaction in patients treated with Tridil is headache. Please see the following page for a brief summary of prescribing information. Note: Tridil is a potent drug and must be diluted before infusion.

For additional information, contact the Medical Services Department, American Critical Care, division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

2. Baaske DM, et al: Administration set suitable for use with intravenous nitroglycerin. *Am J Hosp Pharm* 1982;39:121-122.

TRIDIL® (nitroglycerin) SYSTEM

American Critical Care

TRIDIL® (nitroglycerin)

Brief Summary of Full Prescribing Information

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET® an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION

TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

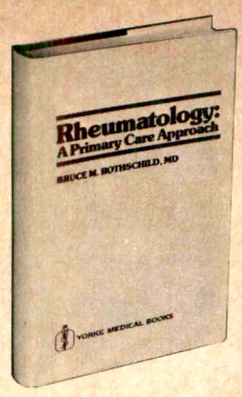
There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED

NDC 0094-0090-05, 25 mg-5 ml ampul. NDC 0094-0090-10, 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

December 1981

Distributed by
American Critical Care
Division of
American Hospital Supply Corporation
McGaw Park IL 60085



The Diagnosis and Treatment Oriented Approach to Rheumatology with the Primary Care Physician in Mind

Rheumatology

A Primary Care Approach

Written by:

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Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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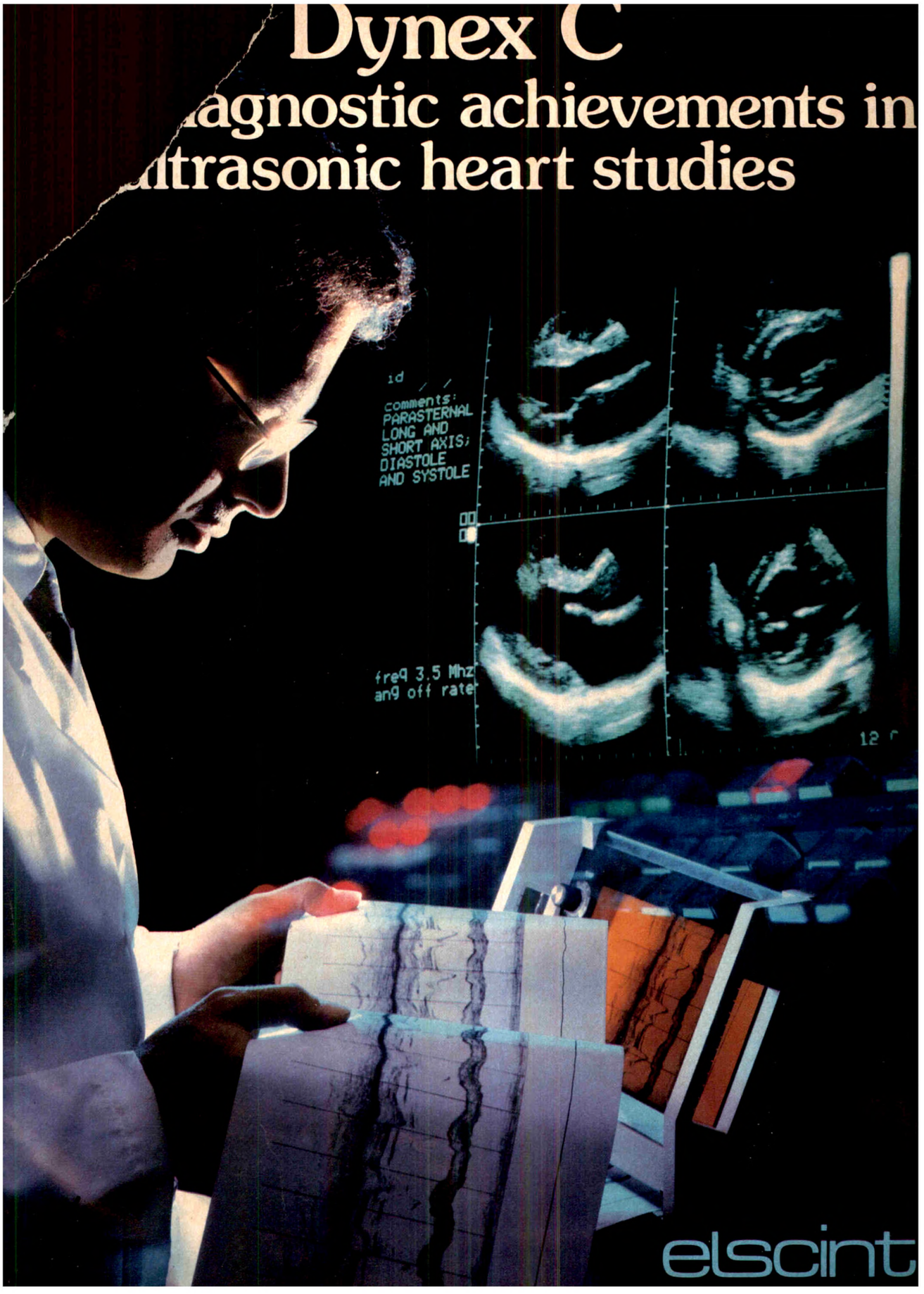
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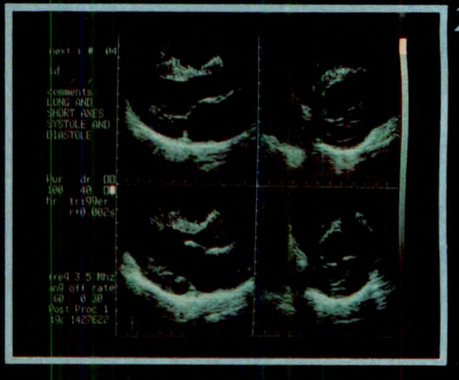

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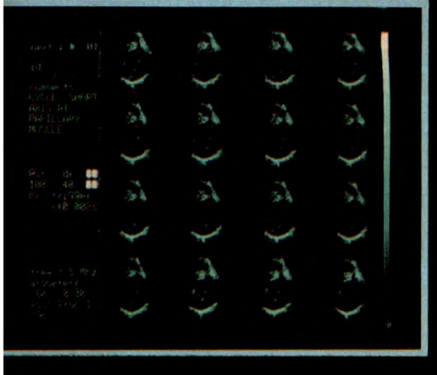

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The CCRM is an exclusive Dynex/C feature for viewing fast sequential 2-D cardiac events, or a complete heart cycle.

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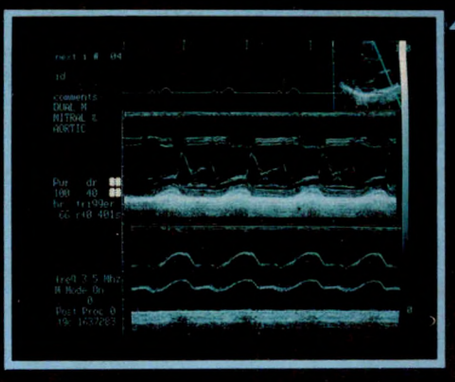

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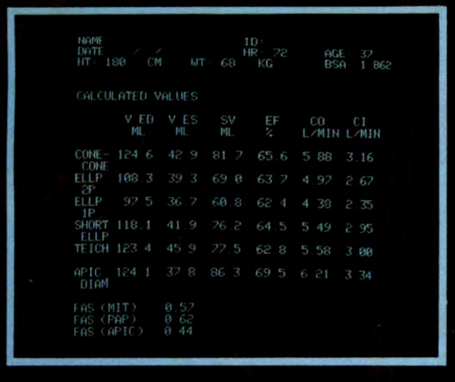

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INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decre excretion of quinidine
With coumarin anticoagulants	Reduction of clotting factor concentration
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
With digoxin	Increased plasma concentrations of dig (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases wh the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: T drug should be used with caution due to excretion of the quinidine in breast milk. AD REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headach disturbed vision) may appear in sensitive patients after a single dose of the drug. GAST TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Wide complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (inclu tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypote TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpu cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, de syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision blurred vision, disturbed color perception, reduced vision field, photophobia, dig blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthm vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Information.

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